(11)Publication number : 09-059258
(43)Date of publication of application : 04.03.1997

(51)Int.Cl. C07D233/88
C07D235/30
C07D263/48
C07D263/58
C07D277/42
C07D277/82
C07D405/06
C07D405/12
C07D417/06
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A61K 31/415
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A61K 31/42
A61K 31/425

(21)Application number : 07-225989
(22)Date of filing : 11.08.1995

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(54) GUANIDYL DERIVATIVE

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a new guanidyl derivative, having excellent suppressing actions on the Maillard reaction and antioxidant actions in combination and further high safety and useful for treatment and/or prevention of diabetic complications, atherosclerosis, etc.
SOLUTION: This guanidyl derivative of formula I {Z is S, O or NR2 (R" is H or a 1-4C alkyl); R1 is H, a 1-4C alkyl or a 2-5C acyl; A is a single bond, a 1-8C alkylene, etc.; ring D group is a group of formula II [R3 is H, a 1-4C


I

II

III

IV

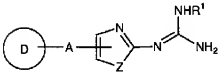
alkyl or a 2-5C acyl; (1) is 0 or 1-10; R4 is a 1-4C alkyl; (p) is 0 or 1-2], formula III [R5 is a 1-7C alkyl, a halogen, etc.; (m) is 0 or 1-5] or formula IV [R7 is a 1-7C alkyl, phenyl, etc.; (n) is 0 or 1-3, etc.]} or its acid addition salt, e.g. a compound of formula V is cited. For example, the compound of formula V is obtained by using a compound prepared from a 3,5-di-t-butyl-4-hydroxybenzaldehyde and methyl triphenylphosphoranylideneacetate as a starting raw material through several steps.

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application]This invention relates to a guanidyl derivative useful as medicine. If it says in more detail, this invention will be 1 general-formula (I).
[Formula 9]



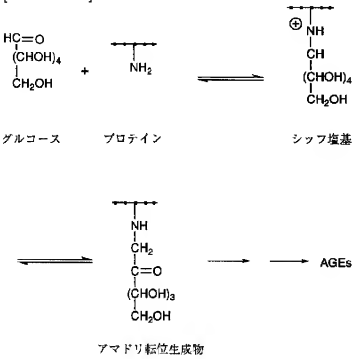
(I)

(all the signs express the same meaning as a postscript among a formula.) -- the guanidyl derivatives shown, those acid addition salt, and 2 -- the manufacturing method of them, and 3 -- it is related with the drugs which contain them as an active principle.
[0002]
[Background of the Invention]Maillard (Maillard) was reported in 1912 paying attention to the phenomenon colored brown, when the mixture of amino acid and reducing sugar was heated [Maillard, L.C., Compt. Rend. Soc. Bio., 72, and 599] (1912). This is based on the reaction of amino acid and sugar, and it suggested that this reaction might occur after that even in the living body. It continued till 1968 and reported that HbA1c which is a small ingredient of hemoglobin increased a larva (Rahbar) in a diabetic [Rahbar.S., Clin. Chim. Acta., 22, and 296] (1968). Combining [behind / with beta chain amino terminal valine / glucose]-with mold which carried out the AMADORI (Amadori) rearrangement-chemical structure of this HbAlc [Koenig, R.J., Blobstein, S.H., & Cerami, A., and J. Biol. Chem., 252, 2992(1977)], And occurring [this reaction]-nonenzymatic (nonenzymatic) [Stevens, V.J., Vlassara, H., Abati, A., & Cerami, A., J.Biol. Chem., and 252, 2998 (1977) It was checked by having clarified] etc. that the Maillard reaction has occurred in the living body.

[0003]A Maillard reaction starts for the amino group of reducing sugar and protein to start the glycosylation (glycosylation), and form Amadori rearrangement output first, as the initial stage. if this advances further -- protein -- crosslinking polymerization [-- this polymer is called glycosylation output (it is written as Advanced Glycosylation Endproducts;AGE.) which ran.] It carries out, the solubility falls, it becomes difficult to receive an operation of protease, fluorescence occurs soon, and it colors brown. Although various mechanisms of AGE generation are advocated, according to Brown Lee (Brownlee) and others, it is as follows, for example (Brownlee, M. et al., Science, 232, and 1629 (1986)).

[0004]

[Formula 10]



[0005]Although a Maillard reaction is a phenomenon seen also in a healthy person, in the diabetic going up and the late protein part of a metabolic turnover, the blood sugar level is seen notably. For example, By hemoglobin, a diabetes-mellitus mouse 2.7 of a normal mouse. Double glycosylation has taken place and [Monnier and V.M. et al. and the Maillard. Reaction in Foods and Nutrition, ACS Symposium Series, 215, 432, Am. Chem. Soc., Washington D.C. (1983)], Glycosylation is accelerating [in / in serum albumin / a diabetic] [Guthrow, C.E. et al., and Proc. Natl. Acad. Sci. U.S.76 and 4258] (1979). The serum protein furthermore glycosylated. Thing [Monnier and V.M. et al. in which typical diabetic kidney trouble appears, Clin. Endocrinol. Metab., 11, and 431] (1982) have turned out to inject intravenously over 12 weeks repeatedly to a mouse.

[0006]They are crystalline ** of an eyeball lens, and special protein which will not carry out a metabolic turnover at all once it biosynthesizes. This thing [that change arises in a spacial

configuration, an enzyme participates in an intramolecular sulfhydryl group, and an SS linkage will be formed and will polymers-ize if it sets crystalline and glycosylation takes place] was accepted. In the case of the diabetes-mellitus student cataract of a rat, the combination with glucose reaches also normal 10 times, and an intramolecular SS linkage also increases it [Monnier, V.M. & Cerami, A. Clin, Endocrinol. Metab, 11, and 431] (1982).

[0007]Coloring of a polymerization, insolubilization, fluorescence generating, yellow - brown has taken place with crystalline glycosylation, Such change coincides with change of the lens by aging well [Chiou, S.H., Chylack, L.T.Jr., Tung, W.H., & Bunn, F., and J. Biol. Chem.256 and 5176] (1981).

[0008]The collagen which exists in connective tissue, and elastin are protein which is rich in lysine and hydroxylysine, A metabolic turnover is also late and Renal glomerular basement membrane, Existence of a connective with glucose is found out by ****** etc., and [Monnier, V.M., Stevens, V.J., & Cerami, A., Maillard Reactions in Food, and Prog. Food Nutr. Sci.5, 315, Pergamon Press, London], To hardening of a blood vessel wall. [Rosenburg,H., Modrak,J.B., Hassing,J.M., Al-Turk,W.A., & Stohs,S.J., Biochem. Biophys. Res. Commun.,91 considered that there is ******, 498 (1979)]. Nonenzymatic glycosylation of nerve myelin protein can be considered as a cause of diabetic diseases of the nervous system [Monnier, V.M. et al., and Clin. Endocrinol. Metab.11 and 431] (1982).

[0009]Thus, it is thought that the Maillard reaction is participating not only in diabetic various complication but in various diseases accompanying aging (aging). It is reported by the latest research that the free radical may be participating in glycosylation of protein [Diabete & Metabolism (Paris), 14, and 25-30 (1988)].

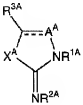
[0010]

[Description of the Prior Art]Search of the substance which checks a Maillard reaction these days is performed on the basis of the above backgrounds. For example, in in vitro (in vitro) the aminoguanidine, Brown Lee and others, It was shown preventing a Maillard reaction and that generation of AGE in an arterial wall will be controlled if a diabetical rat is further medicated with aminoguanidine [Brownlee, M. et al., Science, 232, and 1629] (1986). And the amino group (it combined with the guanidino group) of the aminoguanidine which is a nucleophilicity hydrazine compound as the operation mechanism blocks the activity carbonyl group in Amadori rearrangement output, and suppose that it is it for preventing that crosslinking polymerization of the Amadori rearrangement output is carried out further.

[0011]Furthermore, in a JP,62-142114,A specification. The constituent which controls generation of the secondary glycosylation end product which consists of a compound which has an active nitrogen content group (amino group combined with the guanidino group) which can react to the activity carbonyl group in Amadori rearrangement output is suggested, Specifically, aminoguanidine, alpha-hydrazinohistidine, and lysine are indicated.

[0012]In a JP,7-133264,A specification, it is a general formula (A).

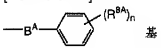
[Formula 11]



(A)

[0013](R^{1A} among a formula a hydrogen atom, a low-grade alkoxy carbonyl low-grade alkyl group, etc.) [express and] R^{2A} is an amino group, a substitution phenyl slufonyl amino group, or a -N=R^{4A} group (among a basis). R^{4A} A low-grade alkylidene group and low-grade cyclo alkylidene group, A phenyl low-grade alkylidene group etc. are expressed. Express and R^{3A} Hydrogen atom, A low-grade alkyl group, low-grade alkenyl group, and phenyl low-grade alkoxy low-grade alkyl group, The unsaturation low-grade heterocycle low-grade alkyl group of a phenyl group, 5 members, or 6 members which has had a hydroxyl group, -a N(R^{6A})R^{7A} group (the inside of a basis, and R^{6A} -- a low-grade alkyl group.) expressing a carboxy low-grade alkyl group, a low-grade alkoxy carbonyl low-grade alkyl group, a 6-hydroxy-2,5,7,8-tetramethyl 2-chromanyl methyloxy group, etc., R^{7A} expresses a hydrogen atom or a low-grade alkyl group. Or [0014]

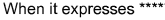
[Formula 12]



B^A expresses a low-grade alkylene group among a basis -- R^{8A} -- a hydroxyl group. A nitro group, an amino group, a halogen atom, a low-grade alkyl group, a lower alkoxy group, A phenoxy group, phenyl low-grade alkyl group, low-grade alkylthio group, and phenyl low-grade alkylthio group etc. are expressed, n expresses 0, or 1-3. Expressing, X^A expresses -S- or -N(R^{10A})- (R^{10A} expresses a hydrogen atom or a low-grade alkoxy carbonyl low-grade alkyl group.), [0015]

[Formula 13]

When it expresses ********, A^A expresses a carbonyl group, [Formula 14]



When it expresses **********, A^A expresses =C(R^{11A})- (R^{11A} expresses a low-grade alkyl group and low-grade alkoxy carbonyl low-grade alkyl group etc.). The compound shown is

indicated as Maillard reaction inhibitor.

[0016]

[Objects of the Invention]This invention persons had the depressant action outstanding to the Maillard reaction, and they inquired so that they may find out a new compound with high safety, and they found out that the guanidyl derivative shown by general formula (I) attained the purpose. That this derivative also has an antioxidant action also found out.

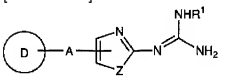
[0017]

[Description of the Prior Art]The guanidyl derivative of this invention compound is a new compound which is not known at all until now. When it explains in detail, the compound shown by a formula (A) is a compound which has a thiazole or an imidazole ring among conventional technology. However, the basis replaced by the 2nd place of those rings is hydrazino (when R^{2A} is an amino group) or a substitution hydrazino group (when R^{2A} is a substitution phenyl slufonyl amino group or $-N=R^{4A}$). It is a compound in which this invention compound makes a guanidyl group indispensable to it at the 2nd place of a thiazole, oxazol, or an imidazole ring. Therefore, this invention compound can be said to be that the compound shown by a formula (A) is a compound which has a completely different structure. It can be said that this invention compound differs from the compound shown by said formula (A) also from the point of having an antioxidant action.

[0018]

[Description of the Invention]This invention is 1 general-formula (I).

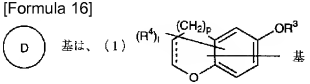
[Formula 15]



(I)

[0019](Z among a formula a sulfur atom, an oxygen atom, or NR^2 (R^2 expresses a hydrogen atom or the alkyl group of C1 - 4 among a basis.)) [express and] R^1 expresses a hydrogen atom, the alkyl group of C1 - 4, or the acyl group of C2 - 5, and A expresses a single bond, the alkylene group of C1 - 8, and the alkylene group of C2 to which one carbon atom is replaced with one sulfur atom or an oxygen atom - 8, [0020]

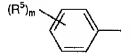
[Formula 16]



(among a basis, R^3 expresses a hydrogen atom, the alkyl group of C1 - 4, or the acyl group of

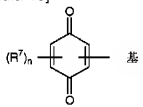
C2 - 5, l expresses 0, or 1-10, R^4 expresses the alkyl group of C1 - 4, and p expresses 0, or 1-2.) [0021]

[Formula 17]

(2)  基

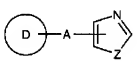
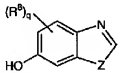
(The inside of a basis and R^5 are an alkyl group of C1 - 7, and OR^6 group (among a basis).) R^6 A hydrogen atom, the alkyl group of C1 - 4, the acyl group of C2 - 5, A phenyl group or the phenyl- C1 - 4 alkyl groups are expressed. Halogen atom, a phenyl group or the phenyl- C1 - 4 alkyl groups, the cycloalkyl group of C5 - 7 or the cycloalkyl C1 of C5 - 7 - 4 alkyl groups are expressed, and m expresses 0, or 1-5. or the above-mentioned ring which the benzene ring has condensed -- or [0022]

[Formula 18]

(3)  基

(R^7 expresses the alkyl group of C1 - 7, a phenyl group or the phenyl- C1 - 4 alkyl groups, the cycloalkyl group of C5 - 7 or the cycloalkyl C1 of C5 - 7 - 4 alkyl groups among a basis, and n expresses 0, or 1-3.) -- it expresses.

[0023]moreover[Formula 19]

式  は、式 

(R^8 expresses the alkyl group of C1 - 7, a phenyl group or the phenyl- C1 - 4 alkyl groups, the cycloalkyl group of C5 - 7 or the cycloalkyl C1 of C5 - 7 - 4 alkyl groups among a formula, and q expresses 0, or 1-3.) -- it expresses.

[0024]However, a sulfur atom or an oxygen atom among (i)A, [Formula 20]

It is alike, does not join together directly and is (ii).

[Formula 21]

In ** (1), a sulfur atom or an oxygen atom among A. [Formula 22]

it is alike and does not join together directly. the guanidyl derivatives shown, those acid addition salt, and 2 -- the manufacturing method of them, and 3 -- it is related with the drugs which contain them as an active principle.

[0025]The alkyl groups of C1 shown by R^1, R^2, R^3, R^4, and R^6 - 4 are methyl, ethyl, propyl, butyl groups, and these isomer groups among general formula (I). The acyl groups of C2 shown by R^1, R^3, and R^6 - 5 are acetyl, propionyl, butyryl, valeryl groups, and these isomer groups among general formula (I). The phenyl- C1 shown by R^5, R^6, R^7, and R^8 - 4 alkyl groups are methyl, ethyl, the propyl and the butyl groups which were replaced by one phenyl group, and these isomer groups among general formula (I). The alkyl groups of C1 shown by R^5, R^7, and R^8 - 7 are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl groups, and those isomer groups among general formula (I).

[0026]The alkylene groups of C1 shown by A - 8 are methylene, ethylene, trimethylene, tetramethylen, pentamethylene, hexamethylene, heptamethylene, octamethylene groups, and these isomer groups among general formula (I). One carbon atom shown by A among general formula (I) with the alkylene group of C2 which replaced one sulfur atom or an oxygen atom - 8 Ethylene, Trimethylene, tetramethylen, pentamethylene, hexamethylene, heptamethylene, an octamethylene group, and one carbon atom in these isomer groups replace a sulfur atom or one oxygen atom. As a halogen atom shown by R^5, fluoride, chlorine, bromine, and iodine are mentioned among general formula (I).

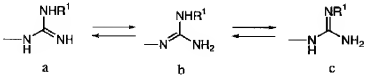
[0027]In this invention, it points especially in the inside of a specification, and a structural formula, and as long as there is nothing, an isomer includes this all. For example, the thing of a straight chain and the thing of a branched chain are contained in an alkyl group, an alkylene group, and an alkenylene group, and the double bond under double bond in an alkenylene group contains what is E, Z, and EZ mixture. The isomer produced by existence of asymmetric carbon atoms in case the alkyl group of a branched chain exists is also contained.

[0028]Inside of this invention, [Formula 23]

As it comes out and the basis shown is shown below, tautomerism exists.

[0029]

[Formula 24]



[0030]It depends, [Formula 25]

It comes out and the basis shown expresses all the bases of the above-mentioned a, b, and c.

[0031]

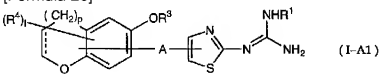
[Salt] The compound shown by general formula (I) is changed into acid addition salt by request by a publicly known method. As for acid addition salt, it is preferred that they are nontoxic and water solubility. As suitable acid addition salt, for example A hydrochloride, the hydrobromate, hydrogen iodide acid chloride, Sulfate, an phosphate, an inorganic acid salt like a nitrate or acetate, a lactate, A tartrate, a benzoate, citrate, methanesulfon acid chloride, an ethane-sulfonic-acid salt, a benzenesulfonic acid salt, a toluenesulfonic acid salt, an isethionic acid salt, a glucuronic acid salt, and organic acid salt like gluconate are mentioned. Acid addition salt is obtained by making the compound shown by general formula (I) react to desired acid the amount of theories every in a publicly known method, for example, a suitable solvent.

[0032]

[The concrete compound of this invention] As a desirable compound of this invention, the following general formulas (I-A1), (I-A2), The compound shown by (I-A3), (I-A4), (I-B1), (I-B2), (I-B3), (I-B4), (I-C1), (I-C2), (I-C3), or (I-C4) and the compound of an example are mentioned.

[0033]

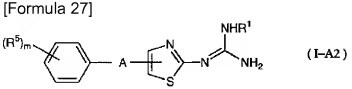
[Formula 26]



(I-A1)

[0034]

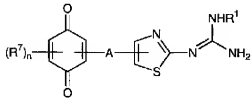
[Formula 27]



(I-A2)

[0035]

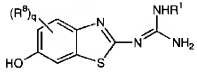
[Formula 28]



(I-A3)

[0036]

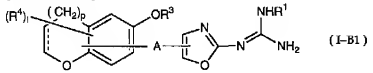
[Formula 29]



(I-A4)

[0037]

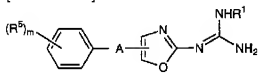
[Formula 30]



(I-B1)

[0038]

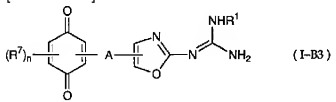
[Formula 31]



(I-B2)

[0039]

[Formula 32]



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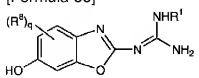
[0040]

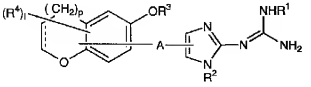
[Formula 33]



(I-B4)

[0041]

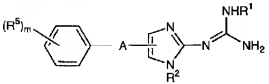
[Formula 34]



(I-C1)

[0042]

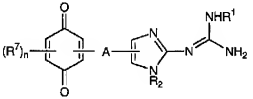
[Formula 35]



(I-C2)

[0043]

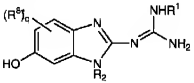
[Formula 36]



(I-C3)

[0044]

[Formula 37]



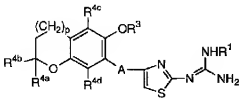
(I-C4)

[0045]As a concrete compound, the compound shown in the following tables 1-24 and the compound of an example are mentioned. Me expresses a methyl group among front, t-Bu expresses a tertiary-butyl group, Ph expresses a phenyl group, and Bz expresses benzyl.

[0046]

[Table 1]

表1



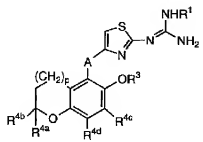
(I-A11)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0047]

[Table 2]

表2



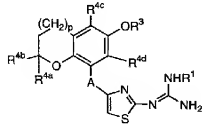
(I－A12)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0048]

[Table 3]

表3



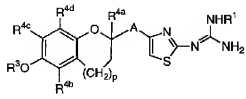
(I-A13)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0049]

[Table 4]

表4



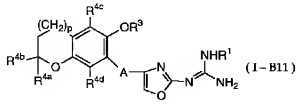
(I-A14)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_2SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0050]

[Table 5]

表5



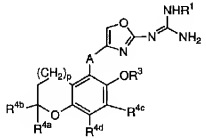
(I-B11)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0051]

[Table 6]

表 6



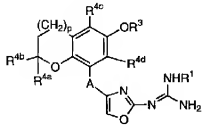
(I－B12)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_2SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0052]

[Table 7]

表7



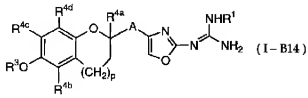
(I－B13)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0053]

[Table 8]

表 8



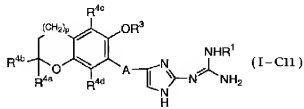
(I-B14)

	R1	p	R4a	R4b	R4c	R4d	R3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_2SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_2OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0054]

[Table 9]

表9



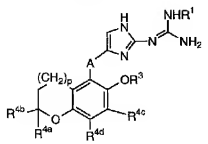
(I-C11)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_2SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0055]

[Table 10]

表１０



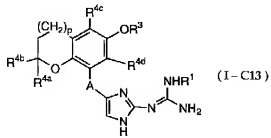
(I-C12)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_2SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0056]

[Table 11]

表１１

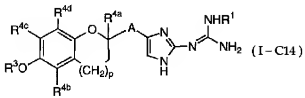


(I－C13)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0057]
[Table 12]

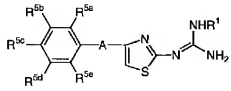
表１２



	R1	p	R4a	R4b	R4c	R4d	R3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0058]
[Table 13]

表１３

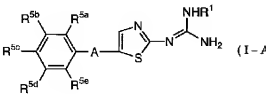


(I－A21)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t－Bu	H	t－Bu	H	$-S(CH_2)_4-$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

[0059]
[Table 14]

表14



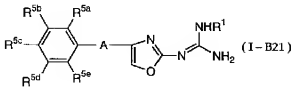
(I-A22)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t-Bu	OH	t-Bu	H	$-(CH_2)_2-$
2	H	H	t-Bu	OMe	t-Bu	H	$-(CH_2)_2-$
3	H	H	t-Bu	H	t-Bu	H	$-(CH_2)_2-$
4	H	H	H	t-Bu	H	H	$-(CH_2)_2-$
5	H	H	t-Bu	OH	t-Bu	H	$-(CH_2)_4-$
6	H	H	t-Bu	OMe	t-Bu	H	$-(CH_2)_4-$
7	H	H	t-Bu	H	t-Bu	H	$-(CH_2)_4-$
8	Me	H	t-Bu	OH	t-Bu	H	$-(CH_2)_4-$
9	Me	H	t-Bu	OMe	t-Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t-Bu	OH	t-Bu	H	$-S(CH_2)_2-$
17	H	H	t-Bu	OMe	t-Bu	H	$-S(CH_2)_2-$
18	H	H	t-Bu	H	t-Bu	H	$-S(CH_2)_4-$
19	H	H	t-Bu	OH	t-Bu	H	$-S(CH_2)_4-$
20	H	H	t-Bu	H	t-Bu	H	$-O(CH_2)_4-$

[0060]

[Table 15]

表15

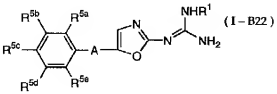


(I-B21)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t-Bu	OH	t-Bu	H	$-(CH_2)_2-$
2	H	H	t-Bu	OMe	t-Bu	H	$-(CH_2)_2-$
3	H	H	t-Bu	H	t-Bu	H	$-(CH_2)_2-$
4	H	H	H	t-Bu	H	H	$-(CH_2)_2-$
5	H	H	t-Bu	OH	t-Bu	H	$-(CH_2)_4-$
6	H	H	t-Bu	OMe	t-Bu	H	$-(CH_2)_4-$
7	H	H	t-Bu	H	t-Bu	H	$-(CH_2)_4-$
8	Me	H	t-Bu	OH	t-Bu	H	$-(CH_2)_4-$
9	Me	H	t-Bu	OMe	t-Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t-Bu	OH	t-Bu	H	$-S(CH_2)_2-$
17	H	H	t-Bu	OMe	t-Bu	H	$-S(CH_2)_2-$
18	H	H	t-Bu	H	t-Bu	H	$-S(CH_2)_4-$
19	H	H	t-Bu	OH	t-Bu	H	$-S(CH_2)_4-$
20	H	H	t-Bu	H	t-Bu	H	$-O(CH_2)_4-$

[0061]
[Table 16]

表16

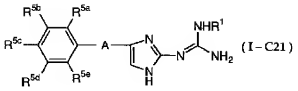


(I－B22)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t－Bu	H	t－Bu	H	$-S(CH_2)_4-$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

[0062]
[Table 17]

表17



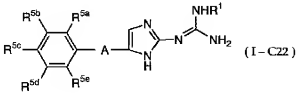
(I-C21)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t-Bu	OH	t-Bu	H	$-(CH_2)_2-$
2	H	H	t-Bu	OMe	t-Bu	H	$-(CH_2)_2-$
3	H	H	t-Bu	H	t-Bu	H	$-(CH_2)_2-$
4	H	H	H	t-Bu	H	H	$-(CH_2)_2-$
5	H	H	t-Bu	OH	t-Bu	H	$-(CH_2)_4-$
6	H	H	t-Bu	OMe	t-Bu	H	$-(CH_2)_4-$
7	H	H	t-Bu	H	t-Bu	H	$-(CH_2)_4-$
8	Me	H	t-Bu	OH	t-Bu	H	$-(CH_2)_4-$
9	Me	H	t-Bu	OMe	t-Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t-Bu	OH	t-Bu	H	$-S(CH_2)_2-$
17	H	H	t-Bu	OMe	t-Bu	H	$-S(CH_2)_2-$
18	H	H	t-Bu	H	t-Bu	H	$-S(CH_2)_4-$
19	H	H	t-Bu	OH	t-Bu	H	$-S(CH_2)_4-$
20	H	H	t-Bu	H	t-Bu	H	$-O(CH_2)_4-$

[0063]

[Table 18]

表１８



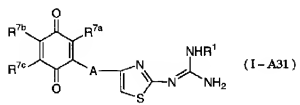
(I－C22)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	－$(CH_2)_2$－
2	H	H	t－Bu	OMe	t－Bu	H	－$(CH_2)_2$－
3	H	H	t－Bu	H	t－Bu	H	－$(CH_2)_2$－
4	H	H	H	t－Bu	H	H	－$(CH_2)_2$－
5	H	H	t－Bu	OH	t－Bu	H	－$(CH_2)_4$－
6	H	H	t－Bu	OMe	t－Bu	H	－$(CH_2)_4$－
7	H	H	t－Bu	H	t－Bu	H	－$(CH_2)_4$－
8	Me	H	t－Bu	OH	t－Bu	H	－$(CH_2)_4$－
9	Me	H	t－Bu	OMe	t－Bu	H	－$(CH_2)_4$－
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	－$S(CH_2)_2$－
17	H	H	t－Bu	OMe	t－Bu	H	－$S(CH_2)_2$－
18	H	H	t－Bu	H	t－Bu	H	－$S(CH_2)_4$－
19	H	H	t－Bu	OH	t－Bu	H	－$S(CH_2)_4$－
20	H	H	t－Bu	H	t－Bu	H	－$O(CH_2)_4$－

[0064]

[Table 19]

表１９



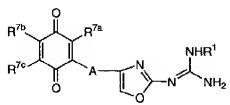
(I－A31)

	R^1	R^{7a}	R^{7b}	R^{7c}	A
1	H	Me	Me	Me	－$(CH_2)_2$－
2	Me	Me	Me	Me	－$(CH_2)_2$－
3	H	Me	Me	Me	－$(CH_2)_4$－
4	H	Me	Me	Me	－$S(CH_2)_4$－
5	H	Me	Me	Me	－$O(CH_2)_4$－

[0065]

[Table 20]

表２０



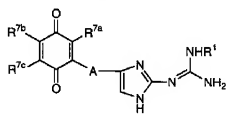
(I－B31)

	R^1	R^{7a}	R^{7b}	R^{7c}	A
1	H	Me	Me	Me	$-(CH_2)_2-$
2	Me	Me	Me	Me	$-(CH_2)_2-$
3	H	Me	Me	Me	$-(CH_2)_4-$
4	H	Me	Me	Me	$-S(CH_2)_4-$
5	H	Me	Me	Me	$-O(CH_2)_4-$

[0066]

[Table 21]

表２１



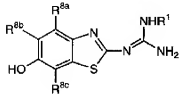
(I－C31)

	R^1	R^{7a}	R^{7b}	R^{7c}	A
1	H	Me	Me	Me	$-(CH_2)_2-$
2	Me	Me	Me	Me	$-(CH_2)_2-$
3	H	Me	Me	Me	$-(CH_2)_4-$
4	H	Me	Me	Me	$-S(CH_2)_4-$
5	H	Me	Me	Me	$-O(CH_2)_4-$

[0067]

[Table 22]

表２２



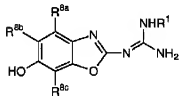
(I－A41)

	R^1	R^{8a}	R^{8b}	R^{8c}
1	H	Me	Me	Me
2	Me	Me	Me	Me
3	H	Me	t－Bu	t－Bu
4	H	Me	Ph	Me
5	H	Me	Bz	Me

[0068]

[Table 23]

表２３



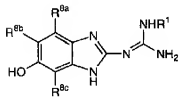
(I－B41)

	R^1	R^{8a}	R^{8b}	R^{8c}
1	H	Me	Me	Me
2	Me	Me	Me	Me
3	H	Me	t－Bu	t－Bu
4	H	Me	Ph	Me
5	H	Me	Bz	Me

[0069]

[Table 24]

表２４



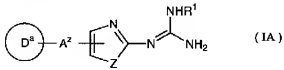
(I－C41)

	R^1	R^{8a}	R^{8b}	R^{8c}
1	H	Me	Me	Me
2	Me	Me	Me	Me
3	H	Me	t－Bu	t－Bu
4	H	Me	Ph	Me
5	H	Me	Bz	Me

[0070]

[Methods for Producing the Invented Chemical Compound]The inside of this invention compound shown by general formula (I), (1) general formula (IA)

[Formula 38]



(IA)

[0071]Inside of [type, [Formula 39]

** [Formula 40]

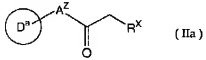
It is although the same meaning is expressed, [Formula 41]

The basis which inner R^3 can remove from the alkyl group of C1 - 4, the acyl group of C2 - 5, or acid. Express (for example, the alkoxyalkyl group of C2 - 4), and R^6 The alkyl group of C1 - 4, Although a basis (for example, alkoxyalkyl group of C2 - 4) removable from the acyl group, the phenyl group, the phenyl- C1 - 4 alkyl groups, or acid of C2 - 5 shall be expressed and A^Z expresses the same meaning as A, a sulfur atom should pass alkylene. [Formula 42]

Except for the case where it is alike and has joined together, other signs express the same meaning as the above. The compound shown by] is a general formula (IIa).

[0072]

[Formula 43]



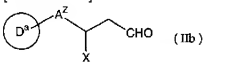
(IIa)

(R^X expresses a halogen atom or an acetyloxy group among a formula, and other signs

express the same meaning as the above.) -- or general formula (IIb)

[0073]

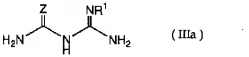
[Formula 44]



(IIb)

(X express a halogen atom among a formula and other signs express the same meaning as the above.) -- the compound shown and general formula (IIIa)

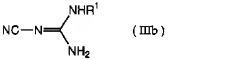
[Formula 45]



(IIIa)

(all the sign expresses the same meaning as the above.) -- the compound shown or general formula (IIIb)

[Formula 46]

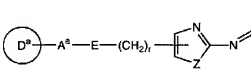


(IIIb)

(all the sign expresses the same meaning as the above.) -- when it is a basis which is made to react to the compound shown or R^3 or R^6 can remove from acid, it can manufacture by performing acid treatment succeedingly.

[0074]The inside of this invention compound shown by (2) general-formula (I), a general formula (IB)

[Formula 47]

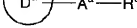


(IB)

[0075](A^a expresses the alkylene group of C1 - 6 among a formula, E expresses a sulfur atom or an oxygen atom, r expresses the integer of 1-6, and other signs express the same meaning as the above.) However, the total number of the carbon atom of A^a and r (CH_2) is seven or less. The compound shown is general formula (IV).

[0076]

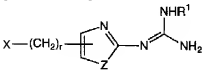
[Formula 48]



(IV)

(R^9 expresses a hydroxyl group or an acetylthio group among a formula, and other signs express the same meaning as the above.) -- the compound shown and general formula (V)

[Formula 49]

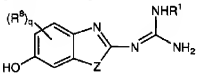


(all the signs express the same meaning as the above among a formula.) -- or [making it react to the compound shown] -- or [Formula 50]

When inner R^3 or R^6 is a basis removable from acid, it can manufacture by performing acid treatment succeedingly.

[0077]The inside of this invention compound shown by (3) general-formula (I), a general formula (IC)

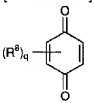
[Formula 51]



(IC)

(all the signs express the same meaning as the above among a formula.) -- the compound shown -- general formula (VI)

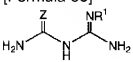
[Formula 52]



(VI)

(all the signs express the same meaning as the above among a formula.) -- the compound shown and general formula (IIIa)

[Formula 53]



(IIIa)

(all the sign expresses the same meaning as the above.) -- it can manufacture by making it react to the compound shown.

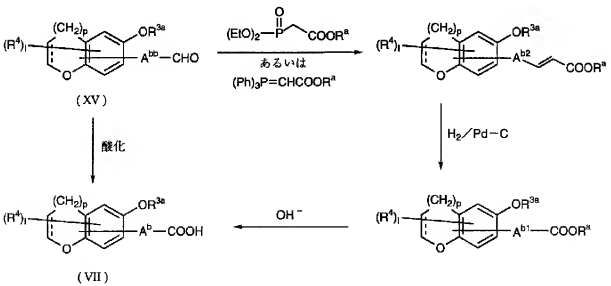
[0078]The reaction of a general formula (IIa), or (IIb) and a general formula (IIIa) is publicly known, for example, is performed by making it react at the temperature of 80-120 ** among an alcoholic solvent (methanol, ethanol, etc.). The reaction of a general formula (IIa), or (IIb) and a general formula (IIIb) is publicly known, for example, is performed by making it react at 10-40 ** among an alcoholic solvent (methanol, ethanol, etc.) and under acid (chloride etc.) existence. Processing by acid is performed among an alcoholic solvent (methanol, ethanol, etc.) by making it react under organic acid (acetic acid, trifluoroacetic acid, etc.) or inorganic acid (chloride, sulfuric acid, etc.) existence. The reaction of general formula (IV) and general formula (V) is publicly known, for example, is performed by making it react in an alcoholic solvent (methanol, ethanol, etc.) and under base (sodium ethoxide etc.) existence. The reaction of general formula (VI) and a general formula (IIIa) is publicly known, for example, is performed by making it react in an alcoholic solvent (methanol, ethanol, etc.) and under acid (chloride etc.) existence.

[0079]The compound shown by the general formula (IIa), (IIb), and (IV) which were used as a starting material can be manufactured by the method shown in the reaction process types 1-8, or a publicly known method, for example, a method given [this] in a specification.

[0080]

[Formula 54]

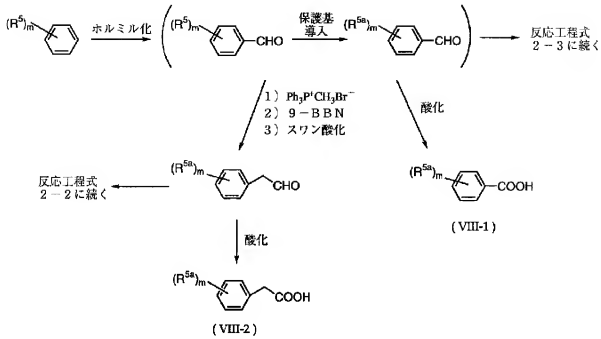
反応工程式1



[0081]

[Formula 55]

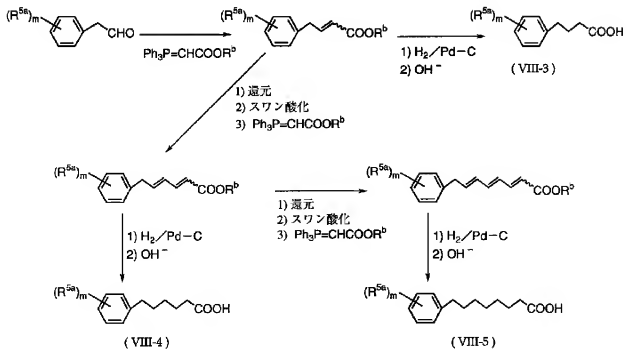
反応工程式２－１



[0082]

[Formula 56]

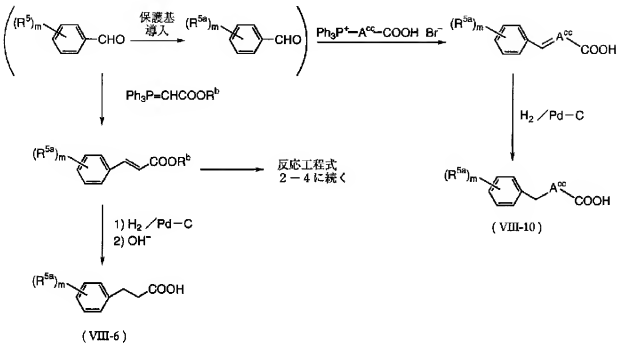
反応工程式２－２



[0083]

[Formula 57]

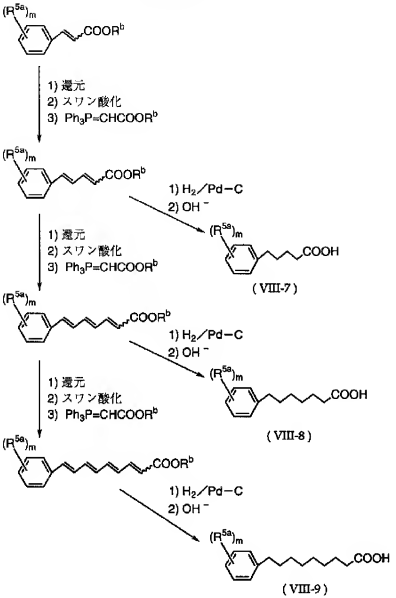
反応工程式２－３



[0084]

[Formula 58]

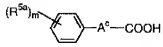
反応工程式２－４



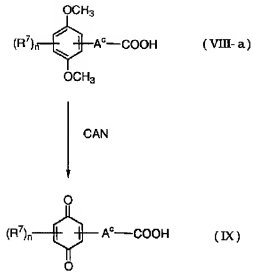
[0085]

[Formula 59]

反応工程式3



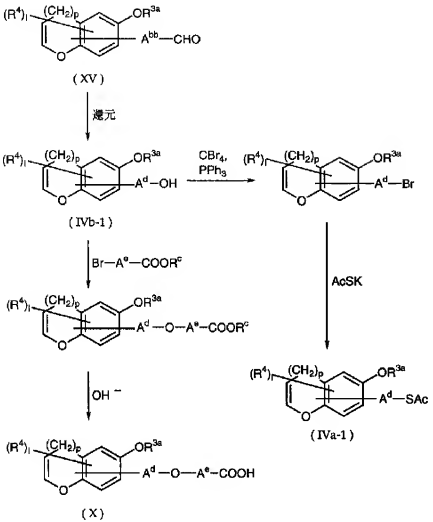
(VIII) = (VIII-1~10)



[0086]

[Formula 60]

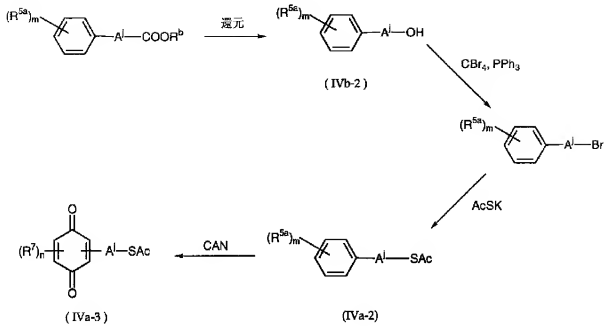
反応工程式4



[0087]

[Formula 61]

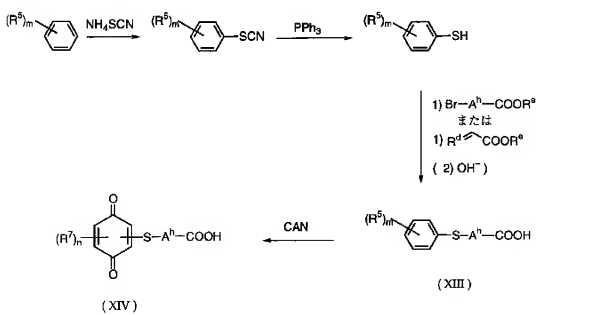
反応工程式5



[0088]

[Formula 62]

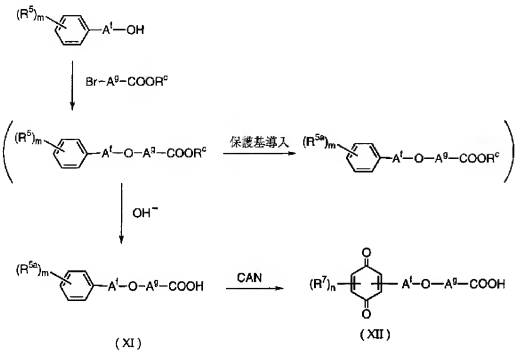
反応工程式6



[0089]

[Formula 63]

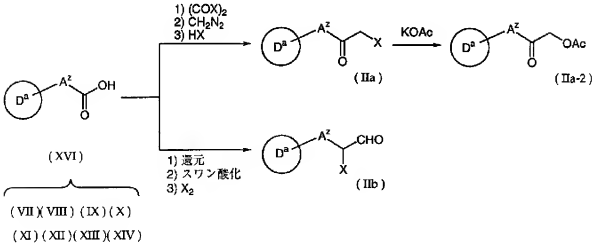
反応工程式7



[0090]

[Formula 64]

反応工程式8



[0091]A^b expresses a single bond or the alkylene group of C1 - 8 among a reaction process type, and A^{b1}, Express the alkylene group of C7 or 8, and A^{b2}, Express the alkylene group of C5 or 6, and A^{bb}, Express a single bond or the alkylene group of C1 - 6, and A^c, Express a

single bond or the alkylene group of C1 - 8, and A^{c1}, Express the alkylene group of C1 - 7, and A^{c2}, Express the alkylene group of C2 - 8, and A^{d}, Express the alkylene group of C1 - 6, and A^{e}, Express the alkylene group (however, the total number of carbon of A^{d} and A^{e} is seven or less.) of C1 - 6, and A^{f}, Express a single bond or the alkylene group of C1 - 6, and A^{g}, The alkylene group (however, the total number of carbon of A^{f} and A^{g} is seven or less.) of C1 - 7 is expressed, A^{h} expresses the alkylene group of C1 - 7, A^{i} expresses the alkylene group of C1 - 6, and A^{j} expresses the alkenylene group of C2 - 8, [0092]The basis which R^{3a} can remove from the alkyl group of C1 - 4, the acyl group of C2 - 5, or acid. Express (for example, the alkoxyalkyl group of C2 - 4), and R^{5a} The alkyl group of C1 - 7, OR^{6a} group (the inside of a basis, and R^{6a} -- the alkyl group of C1 - 4.) The acyl group of C2 - 5, a basis removable from acid (for example, alkoxyalkyl group of C2 - 4), A phenyl group or the phenyl- C1 - 4 alkyl groups are expressed. Express a halogen atom, a phenyl group or the phenyl- C1 - 4 alkyl groups, and R^{b}, Express the alkyl group of C1 - 4, and R^{c}, Express the alkyl group of C1 - 4, and R^{d}, Express a hydrogen atom or the alkyl group of C1 - 5, and R^{e}, express a hydrogen atom or the alkyl group of C1 - 4, Ph expresses a phenyl group, Et expresses an ethyl group, AcSK expresses thiacetic acid potassium, and CAN expresses a cerium ammonium nit rate -- 9-BBN -- Nine - bora -- bicyclo[3.3.1] nonane is expressed.

[0093]The other starting material and each reagent in this invention are publicly known in itself, or can be manufactured by a publicly known method. For example, the manufacturing method of the compound shown by general formula (V) is indicated by the JP,53-147069,A specification. The compound shown by general formula (XV) is indicated by the PCT application number JP 95/No. 294 specification.

[0094]A resultant can be refined by methods using the distillation under the usual refining means, for example, ordinary pressure, or decompression, silica gel, or a magnesium silicate, such as high performance chromatography, thin layer chromatography, column chromatography or washing, and recrystallization. Refining may be performed for every reaction and it may carry out after some ending reaction.

[0095]

[Effect of the Invention]The Maillard reaction inhibitory action of this invention compound was checked by the screening system using various protein and various sugar. For example, it was checked by the screening system described below.

(1) An experimental method lysozyme and fructose are dissolved in 0.2M sodium phosphate buffer solution (pH 7.4) so that it may become the concentration of 10mg [ml] /and 100mM, respectively, After carrying out an incubation for three days at 37 **, the constant rate was taken out and electrophoresis was performed using SDS-PAGE. Under [a fixed quantity /

densitometer / after dyeing and / generated amount / of a dimer / in after electrophoresis and 0.2% Coomassie Brilliant Blue (Coomassie Brilliant Blue) R-250]. It added before the incubation, and this invention compound investigated the depressor effect over the dimer generation in various concentration, and calculated IC_{50} value.

(2) A result is shown in Table 25.

[0096]

[Table 25]

Example number IC_{50}(muM) 1 4.4 1 (1) 2.9 1 (5) 9.2 1 (30) 4.4 1 (37) 1.5 1 (40) 2.71 (44) 5.5

[0097]The antioxidant action of this invention compound was checked by the screening system which investigates the peroxylipid generation depressor effect described below.

(1) Perfusion of the male Sprague Dawley rat made to abstain from food overnight [experimental method] was carried out from the portal vein with the ice-cooled 0.9% sodium chloride aqueous solution under anesthesia, and the hepatic tissue was extracted. It was considered as the homogenate 10% using the 1.15% potassium chloride aqueous solution which ice-cooled the extraction liver. $FeCl_2$200mM was added to obtained homogenate 200microl, and it incubated at 37 ** for 1 hour. In accordance with the method [Analytical Biochemistry, 95, and 351 reference (1979)] of OOKAWA and others (Ohkawa), the generated amount of peroxylipid was measured by the thiobarbituric acid (TBA) method. It added before the incubation, and this invention compound investigated the effect, and computed IC_{50} value.

(2) A result is shown in Table 26.

[0098]

[Table 26]

Example number IC_{50}(muM) 1 3.8 1 (5) 3.7 1 (29) 2.9 1 (32) 1.8 1 (39) 0.82 1 (25) 161 (47) 0.56 1 (41) 0.453 0.96[0099]Table 25 and 26 shows that this invention compound, its nontoxic salt, and its acid addition salt have Maillard reaction inhibitory action and an antioxidant action.

[0100]

[Toxicity] It was checked that it can be used safely [the toxicity of this invention compound is low enough, and / enough] as drugs.

[0101]

[Application in drugs] this invention compounds shown by general formula (I), and those acid addition salt, Since a Maillard reaction is checked, various diabetic complications, for example, coronary artery nature heart disease, It is useful to the therapy and/or prevention of peripheral circulatory bisturdance, the cerebrovascular disease, diabetic neurosis, a nephropathy, arteriosclerosis, the arthrosclerosis, a cataract, a retinopathy and the disease caused by aging, for example, atherosclerosis, senile cataract, and cancer. this invention compounds shown by

general formula (I) and those acid addition salt, Since it has an antioxidant action, i.e., the operation which inhibits the reaction of a free radical, peroxylipid production is useful to the therapy and/or prevention of various diseases used as a cause, for example, arteriosclerosis, diabetes mellitus, myocardial infarction, peripheral circulatory bisturdance, the cerebrovascular disease, cancer, inflammation, a digestive system disease, and aging.

[0102]In order to use this invention compounds shown by general formula (I), and those acid addition salt for the above-mentioned purpose, a medicine is usually prescribed for the patient by taking orally or parenteral systemic or locally. Although a dose changes with age, weight, condition, a curative effect, a medication method, processing time, etc., Usually, it is administered orally several times from 1 time per day in 1 mg - 1000 mg per time per one adult, or parenteral administration (it administers intravenously preferably) is carried out several times from 1 time per day in 0.1 mg-100mg per time per one adult. As described above, of course, since a dose is changed on condition of versatility, a quantity smaller than the above-mentioned dose range may be enough as it, and it may be required exceeding the range.

[0103]When prescribing this invention compound for the patient, the injections for the solid constituent for internal use, a liquid composition and other constituents, and parenteral administration, external preparations, suppositories, etc. are used.

[0104]A tablet, a pill, a capsule, powder medicine, a granule, etc. are contained in the solid constituent for internal use. A hard capsule and a soft capsule are contained in a capsule. In such a solid constituent, one or the active substance beyond it is mixed with one inertness diluent, for example, hydroxypropylcellulose, microcrystalline cellulose, starch, a polyvinyl pyrrolidone, and magnesium aluminometasilicate at least. The constituent may contain a solubilizing agent like additive agents other than an inertness diluent, for example, lubricant like magnesium stearate, disintegrator like a calcium carboxymethyl cellulose, glutamic acid, or aspartic acid in accordance with a conventional method. The tunic of a tablet or the pill may be carried out as occasion demands with the film of stomach solubility, such as white soft sugar, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, or an enteric substance, and a tunic may be carried out in two or more layers. The capsule of a substance still like gelatin by which it is absorbed and in which it deals is also included. The liquid composition for internal use may contain the inertness diluent (for example, purified water, ethanol) generally used including an opacifier, a solution agent, suspension, syrups, elixirs, etc. which are permitted in drugs. This constituent may contain a wetting agent, an adjuvant like suspension, the sweetening agent, the flavor agent, the aromatic, and the antiseptic in addition to an inertness diluent. As a constituent of others for internal use, the spray prescribed by a publicly known method in itself is contained including one or the active substance beyond it. This constituent may contain a buffer which gives stabilizer and the isotonicity like sodium

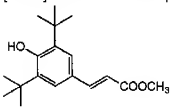
hydrogen sulfite in addition to an inertness diluent, for example, sodium chloride, sodium acid citrate, or citrate. The manufacturing method of spray is written in detail, for example in U.S. Pat. No. 2868691 and the 3095355th item specification.

[0105]As injections for the parenteral administration by this invention, a sterile water or non-aqueous solution agent, suspension, and an opacifier are included. As a water solution agent and suspension, distilled water for injection and a physiological saline are contained, for example. As the solution agent of nonaqueous solubility, and suspension, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80, etc., for example. Such a constituent may also contain an adjuvant still like an antiseptic, a wetting agent, an emulsifier, a dispersing agent, a stabilizing agent, and a solubilizing agent (for example, glutamic acid, aspartic acid). These are sanitized by the combination or the exposure of filtration and a germicide which lets for example, a bacteria suspension filter pass. These manufacture a sterile solid constituent again, and they can also use it for aseptic water or the sterile solvent for injection before use, dissolving. As a constituent of others for parenteral administration, the pessary for the suppositories for the liquids for external use prescribed by a conventional method, paint like ointment, and intrarectal administration and the administration in a vagina, etc. are contained including one or the active substance beyond it.

[0106]

[Related Example(s) and Working Example(s)]Hereafter, although this invention is explained in full detail according to a reference example and an example, this invention is not limited to these. The solvent in the parenthesis indicated in the part of separation by chromatography shows the used developing solvent, and a rate expresses a volume ratio. The inside of the parenthesis indicated in the part of NMR shows the measurement solvent.

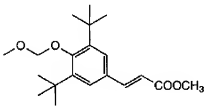
[0107]Reference example 1 [Formula 65]



[0108]Under argon, it flowed back for 1 hour and 3,5-di-t-butyl-4-hydroxybenzaldehyde (11.7g) and the benzene solution (50 ml) of triphenyl phospho RIDEN acetic acid methyl ester (18.4g) were condensed. The residue was refined by column chromatography (ethyl acetate: n-hexane=1:10->5:1), and the title compound (14.1g) which has the following property value was obtained.

TLC:Rf 0.51 (ethyl acetate: n-hexane=1:5).

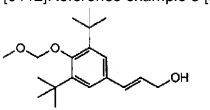
[0109]Reference example 2 [Formula 66]



[0110]The DMF solution (20 ml) of the compound (8.0g) manufactured by the reference example 1 under -78 ** and argon was added to the dimethylformamide (DMF) suspension of sodium hydride (60% content; 1.65g). The mixture was agitated for 15 minutes at 0 **. Methoxymethyl chloride (2.5 ml) was added to the reaction mixture at 0 **, and it agitated for 10 minutes, and agitated at the room temperature further for 2 hours. Sodium hydride (60% content; 0.83g) and methoxymethyl chloride (1.2 ml) were added, and it agitated at the room temperature for 1 hour. Water was added to the reaction solution and ethyl acetate extracted. The organic layer was washed with water and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (8.80g) which has the following property value was obtained.

[0111]TLC:Rf 0.40 (ethyl acetate: n-hexane=1:9) and NMR($CDCl_3$):delta 7.65 (1H, d), 7.44 (2H, s), 6.34 (1H, d), 4.91 (2H, s), 3.80 (3H, s), 3.65 (3H, s), 1.45 (18H, s).

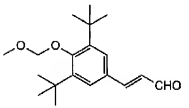
[0112]Reference example 3 [Formula 67]



[0113]The toluene solution (65.7 ml) of 1M diisobutylaluminum hydride was added to the methylene chloride solution (30 ml) of the compound (8.79g) manufactured by the reference example 2 under -78 ** and argon. The mixed solution was agitated for 30 minutes at -78 **. Water was added to the reaction solution, 1N chloride neutralized, and ethyl acetate extracted, after using acidity by citrate. A saturation salt solution, saturated sodium bicarbonate, and a saturation salt solution washed the organic layer one by one, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane=1:6), and the title compound (8.03g) which has the following property value was obtained.

[0114]TLC:Rf 0.11 (ethyl acetate: n-hexane=1:9) and NMR($CDCl_3$):delta 7.30 (2H, s), 6.57 (1H, d), 6.27 (1H, dt), 4.89 (2H, s), 4.30 (2H, s), 3.64 (3H, s), 1.45 (18H, s).

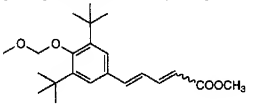
[0115]Reference example 4 [Formula 68]



[0116]Triethylamine (30 ml), dimethyl sulfoxide (DMSO) (25 ml), and a sulfate RIOKISHIDO pyridine complex (16.6g) were added to the methylene chloride solution (25 ml) of the compound (8.0g) manufactured by the reference example 3 under 0 ** and argon. After agitating a mixture for 5 minutes at 0 **, it agitated for 30 minutes at the room temperature further. It is ****** to the mixed solution of ethyl acetate and water about a reaction solution. A saturation salt solution, citrate, a saturation salt solution, saturated sodium bicarbonate, and a saturation salt solution washed the organic layer one by one, with magnesium sulfate, after desiccation, it condensed and the title compound which has the following property value was obtained.

[0117]TLC:Rf 0.80 (ethyl acetate: n-hexane=1:4) and NMR($CDCl_3$):delta 9.68 (1H, d), 7.49 (2H, s), 7.45 (1H, d), 6.65 (1H, d), 4.93 (2H, s), 3.66 (3H, s), 1.46 (18H, s).

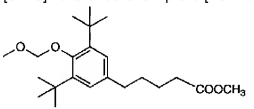
[0118]Reference example 5 [Formula 69]



[0119]Under argon, it flowed back for 13 hours and the compound and the benzene solution (50 ml) of triphenyl phospho RIDEN acetic acid methyl ester (17.52g) which were manufactured by the reference example 4 were condensed. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (8.05g) which has the following property value was obtained.

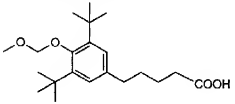
TLC:Rf 0.40 (ethyl acetate: n-hexane =1:10).

[0120]Reference example 6 [Formula 70]

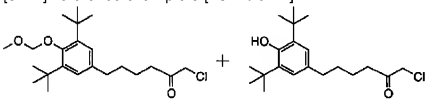


[0121]The methanol solution (20 ml) of the compound (8.04g) manufactured by the reference example 5 and palladium carbon (800 mg) was agitated at the room temperature under

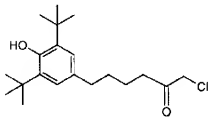
hydrogen gas for 16 hours. Cerite filtration was carried out and the reaction solution was condensed. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (7.30g) which has the following property value was obtained.
TLC:Rf 0.37 (ethyl acetate: n-hexane =1:10).
[0122]Reference example 7 [Formula 71]



[0123]2N sodium hydroxide (35 ml) was added to the methanol solution (10 ml) of the compound (3.65g) manufactured by the reference example 6 at 0 **. At the room temperature, the mixed solution was agitated for 6 hours and condensed. It acidified with 1N chloride and ethyl acetate extracted the residue. The saturation salt solution washed the organic layer, with magnesium sulfate, after desiccation, it condensed and the title compound which has the following property value was obtained.
TLC:Rf 0.07 (ethyl acetate: n-hexane =1:10).
[0124]Reference example 8 [Formula 72]



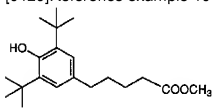
[0125]Oxalyl chloride (1.05 ml) and DMF (three drops) were added to the benzene solution (10 ml) of the compound manufactured by the reference example 7 under 0 ** and argon. The mixed solution was agitated at the room temperature for 1 hour. The reaction solution was condensed and the residue was dissolved in diethylether. At 0 **, it was dropped at it until gas stopped having generated the ethanol solution of diazomethane in the solution, and also it was dropped until gas stopped having generated the 1,4-dioxane (10 ml) solution of 4N chloride at 0 **. The solution was diluted with ethyl acetate, the saturation salt solution washed, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the mixed compound (3.54g) of the title was obtained.
[0126]Reference example 9 [Formula 73]



[0127]Since the compound manufactured by the reference example 8 was a mixture of the thing from which the hydroxyl group is protected, and the thing which is not carried out, it added the 1,4-dioxane solution (10 ml) of 4N chloride to 1,4-dioxane (10 ml) of the mixture, and the mixed solution of water (0.5 ml) at 0 **. The mixed solution was agitated at the room temperature for 12 hours. The reaction solution was condensed and ethyl acetate extracted. The saturation salt solution washed the organic layer and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (3.18g) which has the following property value was obtained.

[0128]TLC:Rf 0.42 (ethyl acetate: n-hexane =1:10), NMR($CDCl_3$): delta 6.96 (2H, s), 5.03 (1H, s), 4.05 (2H, s), 2.62 (2H, t), 2.54 (1H, t), 1.50-1.80 (4H, m), 1.43 (18H, s).

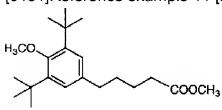
[0129]Reference example 10 [Formula 74]



[0130]Using the compound (3.65g) manufactured by the reference example 6, it was operated like the reference example 9 and the title compound (3.58g) which has the following property value was obtained.

TLC:Rf 0.41 (ethyl acetate: n-hexane =1:10), NMR($CDCl_3$): delta 6.96 (2H, s), 5.03 (1H, s), 3.67 (3H, s), 2.53 (2H, t), 2.35 (1H, t), 1.50-1.80 (4H, m), 1.43 (18H, s).

[0131]Reference example 11 [Formula 75]

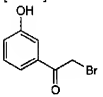


[0132]Sodium hydride (60% content; 1.20g) was added to the DMF solution (25 ml) of the compound (3.20g) manufactured by the reference example 10. Suspension was agitated for 30 minutes at 0 **. Iodination methane (2.49 ml) was added to the reaction mixture at 0 **. The

mixture was agitated at the room temperature for 24 hours. Saturated ammonium chloride was added to the reaction mixture, and ethyl acetate extracted. Saturated ammonium chloride and a saturation salt solution washed the organic layer, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (3.30g) which has the following property value was obtained.

TLC:Rf 0.38 (ethyl acetate: n-hexane =1:10).

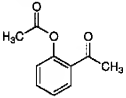
[0133]Reference example 12 [Formula 76]



[0134]Bromine (378microl) was slowly added to acetic acid of a 3'-hydroxyacetophenone (1.0g), and the mixed solution (3.0ml+0.5ml) of the tetrahydro franc (THF). The mixture was agitated at the room temperature for 1.5 hours. The reaction solution was diluted with ethyl acetate, saturated sodium bicarbonate, water, and a saturation salt solution washed one by one, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane=1:5), and the title compound (1.10g) which has the following property value was obtained.

TLC:Rf 0.32 (ethyl acetate: n-hexane=1:3).

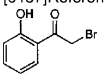
[0135]Reference example 13 [Formula 77]



[0136]Pyridine (1.5 ml), an acetic anhydride (1.5 ml), and 4-dimethylaminopyridine (0.03g) were added to the methylene chloride solution (10 ml) of the 2'-hydroxyacetophenone (1.5g). At the room temperature, the mixed solution was agitated for 3 hours and condensed. The residue was diluted with ethyl acetate, water, 1N chloride, and a saturation salt solution washed one by one, with magnesium sulfate, after desiccation, it condensed and the title compound (2.8g) which has the following property value was obtained.

TLC:Rf 0.15 (ethyl acetate: n-hexane =1:10).

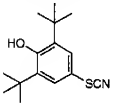
[0137]Reference example 14 [Formula 78]



[0138]The pyridinium star's picture par star's picture (1.58g) was added to the THF solution (10 ml) of the compound (800 mg) manufactured by the reference example 13. The mixture was agitated at the room temperature for 1 hour. The reaction solution was diluted with ethyl acetate, and it washed with water, and condensed after desiccation with magnesium sulfate. After neglecting a residue overnight, it refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (593 mg) which has the following property value was obtained.

TLC:Rf 0.30 (ethyl acetate: n-hexane=1:3).

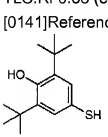
[0139]Reference example 15 [Formula 79]



[0140]After pouring gaseous chlorine into the methanol solution (25 ml) of 2,6-di-t-butylphenol (5.0g) and ammonium thiocyanate (3.9g) at 0 ** for 20 minutes, argon substitution was carried out, and ammonia gas was poured in at 0 ** for 20 minutes, and was agitated for 30 more minutes. The reaction solution was poured out into ice water and the sediment was ****(ed) after neglect overnight. The sediment was refined by column chromatography (ethyl acetate: n-hexane =1:15), and the title compound (5.2g) which has the following property value was obtained.

TLC:Rf 0.38 (ethyl acetate: n-hexane =1:15).

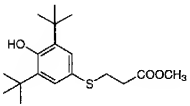
[0141]Reference example 16 [Formula 80]



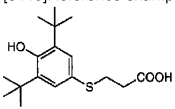
[0142]After adding triphenyl phosphine (4.8g) and water (0.66 ml) to the acetone solution (20 ml) of the compound (4.8g) manufactured by the reference example 15 at 0 **, it agitated at the room temperature for 3 hours. The reaction solution was condensed, the residue was refined by column chromatography (ethyl acetate: n-hexane =1:30), and the title compound (3.0g) which has the following property value was obtained.

TLC:Rf 0.58 (ethyl acetate: n-hexane=1:5).

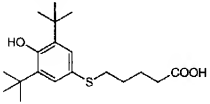
[0143]Reference example 17 [Formula 81]



[0144]Triethylamine (82microl) and methyl acrylate (927microl) were added to the methanol solution (5 ml) of the compound (817 mg) manufactured by the reference example 16, and it agitated for 20 minutes at the room temperature. The reaction solution was condensed, the residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (817 mg) which has the following property value was obtained.
TLC:Rf 0.15 (ethyl acetate: n-hexane =1:20).
[0145]Reference example 18 [Formula 82]



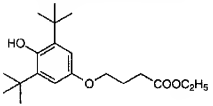
[0146]Lithium hydroxide (528 mg) solution was added to the methanol solution (5 ml) of the compound (815 mg) manufactured by the reference example 17, and it agitated at the room temperature for 1 hour. The reaction solution was condensed. To the residue, in addition, ethyl acetate extracted 1N hydrochloric acid aqueous solution until pH was set to one. Water and a saturation salt solution washed the organic layer, with magnesium sulfate, after desiccation, it condensed and the title compound (776 mg) which has the following property value was obtained.
TLC:Rf 0.34 (ethyl acetate: n-hexane=1:1)
[0147]Reference example 19 [Formula 83]



[0148]Diisopropylethylamine (667microl) and 5-bromine valeric acid (694 mg) were added to the DMF solution (15 ml) of the compound (760 mg) manufactured by the reference example 16, and it agitated at the room temperature overnight. Ice water was added to the reaction solution and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (chloroform: methanol =20:1), and the title compound (485 mg) was

obtained.

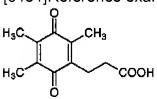
[0149]Reference example 20 [Formula 84]



[0150]Sodium hydride (356 mg) was added to the DMF solution (15 ml) of 2,5-di-tert-butylhydroquinone (1.8g) at 0 **, and 30 between was agitated at the room temperature. 4-bromine ethyl butyrate (1.3 ml) was added to the reaction solution at 0 **, and it agitated at 60 ** overnight. Ice water was added to the reaction solution and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and it dried with magnesium sulfate. The solvent was distilled off, the residue was refined by column chromatography (ethyl acetate: n-hexane =1:30), and the title compound (1.73g) which has the following property value was obtained.

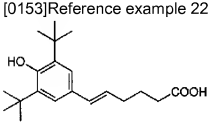
TLC:Rf 0.66 (ethyl acetate: n-hexane=1:3).

[0151]Reference example 21 [Formula 85]



[0152]3,6-dimethoxy- 2,4,5-trimethyl benzaldehyde is used, In the 50% acetonitrile solution (50 ml) of 3-(3,6-dimethoxy- 2,4,5-trimethyl phenyl) propanoic acid (2.07g) produced by making it be the same as that of the reference example 1 -> reference example 6 -> reference example 7. At 0 **, the 50% acetonitrile solution (25 ml) of the cerium ammonium nit rate (9.92g) was added, and it agitated for 15 minutes. The reaction solution was filled with sodium bicarbonate solution, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, it condensed after desiccation with magnesium sulfate, and the title compound (0.91g) was obtained.

[0153]Reference example 22 [Formula 86]

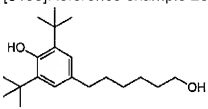


[0154]The DMSO solution (20 ml) suspension of sodium hydride (60% content; 865 mg) was

agitated at 70 ** for 1 hour. The DMSO solution (10 ml) of 5-(triphenyl phosphine) pentanoic acid star's picture (4.78g) was dropped at 10-20 **, and was agitated for 30 minutes at the room temperature. The DMSO solution (10 ml) of 3,5-di-t-butyl-4-hydroxy-benzaldehyde (1.00g) was dropped at 10-20 **, and it agitated at the room temperature overnight. Water was filled with the reaction solution, 2N chloride was added, and JIECHIERU ether extracted. Water and a saturation salt solution washed the organic layer, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane=1:3), and the title compound which has the following property value was obtained.

TLC:Rf 0.15 (ethyl acetate: n-hexane=1:3).

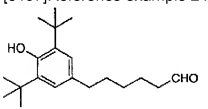
[0155]Reference example 23 [Formula 87]



[0156]The compound produced by operating it like the reference example 6 using the compound manufactured by the reference example 22, The lithium aluminum hydride (30 mg) was added to the THF solution (3 ml) of 6-(3,5-t-butyl-4-hydroxyphenyl)-5-hexene acid (100 mg) at 0 **, and it agitated at the room temperature for 1 hour. The saturation sodium sulfate aqueous solution was dropped at the reaction solution, and after churning, it sodium-sulfate-****(ed) and filtered. The filtrate was condensed, the residue was refined by column chromatography (ethyl acetate: n-hexane=1:5->1:3), and the title compound which has the following property value was obtained.

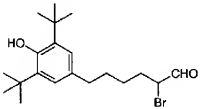
TLC:Rf 0.20 (ethyl acetate: n-hexane=1:3).

[0157]Reference example 24 [Formula 88]

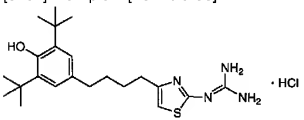


[0158]The methylene chloride solution (1 ml) of oxalyl chloride (0.025 ml) was cooled at -70 **. The methylene chloride solution (1 ml) of DMSO (0.04 ml) was dropped there. The mixed solution was agitated for 10 minutes. The methylene chloride solution (1 ml) of the compound manufactured by the reference example 23 was added to the reaction solution, and it agitated for 30 minutes. Triethylamine (0.2 ml) was added to the reaction solution, the dry ice bath was removed, and it agitated for 30 minutes. Ether extracted the reaction solution. Water and a

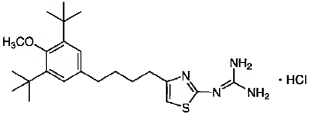
saturation salt solution washed the organic layer, with magnesium sulfate, after desiccation, it condensed and the title compound which has the following property value was obtained.
TLC:Rf 0.59 (ethyl acetate: n-hexane=1:3).
[0159]Reference example 25 [Formula 89]



[0160]The chloroform fluid (0.25 ml) of bromine (0.07 ml) was dropped at the chloroform fluid (10 ml) of the compound manufactured by the reference example 24 at -20 **. The mixed solution was returned to the room temperature after 1-hour churning at -20 **. It cooled at -20 ** again, the chloroform fluid (0.12 ml) of bromine (0.04 ml) was dropped, and it agitated for 30 minutes at -20 **. The reaction solution was condensed, the residue was refined by column chromatography (ethyl acetate: n-hexane =1:30), and the title compound which has the following property value was obtained.
TLC:Rf 0.43 (ethyl acetate: n-hexane =1:10).
[0161]Example 1 [Formula 90]



[0162]The methanol solution (20 ml) of the compound (2.0g) manufactured by the reference example 9 and guanidino thiourea (662 mg) was flowed back for 12 hours. The reaction solution was condensed, it recrystallized in diethylether, and the title compound (2.42g) which has the following property value was obtained.
[0163]TLC:Rf 0.34 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$): delta 6.96 (2H, s), 6.46 (1H, s), 5.04 (1H, s), 2.67 (2H, t), 2.54 (2H, t), 1.70-1.62 (4H, m), 1.43 (18H, s).
[0164]Example 1 (1)
[Formula 91]

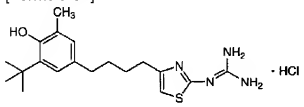


[0165]Using the compound manufactured by the reference example 11, it was operated like the reference example 7 -> reference example 8 -> example 1, and the title compound which has the following property value was obtained.

TLC:Rf 0.33 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$): delta 7.02 (2H, s), 6.46 (1H, s), 3.67 (3H, s), 2.66 (2H, t), 2.55 (2H, t), 1.73-1.65 (4H, m), 1.41 (18H, s).

[0166]Example 1 (2)

[Formula 92]

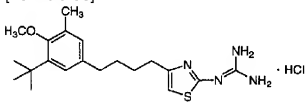


[0167]Using corresponding aldehyde, it was operated like the reference example 1 -> reference example 2 -> reference example 3 -> reference example 4 -> reference example 5 -> reference example 6 -> reference example 7 -> reference example 8 -> reference example 9 -> example 1, and the title compound which has the following property value was obtained.

TLC:Rf 0.34 (ethyl acetate: acetic acid : water =20:1:1), NMR. ($CDCl_3$) :. delta 6.91(1H,d), 6.79 (1H,d), 6.45(1H,s), 4.89(1H,s), 2.64(2H,t), 2.52(2H,t), 2.24(3H,s), 1.68-1.58(4H,m), 1.39 (9H, s).

[0168]example 1 (3)

[Formula 93]

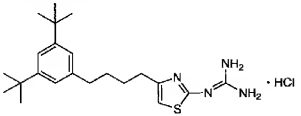


[0169]Using corresponding aldehyde, it was operated like the reference example 1 -> reference example 2 -> reference example 3 -> reference example 4 -> reference example 5 -> reference example 6 -> reference example 10 -> reference example 11 -> reference example 7 -> reference example 8 -> example 1, and the title compound which has the following property value was obtained.

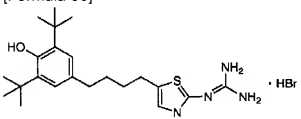
TLC:Rf 0.35 (ethyl acetate: acetic acid : water =20:1:1), NMR. ($CDCl_3$) :. delta 6.94(1H,d), 6.85 (1H,d), 6.46(1H,s), 3.75(3H,s), 2.66(2H,t), 2.54(2H,t), 2.29(3H,s), 1.70-1.60(4H,m), 1.37 (9H, s).

[0170]example 1 (4)

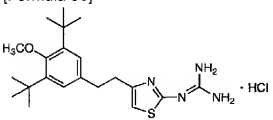
[Formula 94]



[0171]Using corresponding aldehyde, it was operated like the reference example 1 -> reference example 3 -> reference example 4 -> reference example 5 -> reference example 6 -> reference example 7 -> reference example 8 -> example 1, and the title compound which has the following property value was obtained.
TLC:Rf 0.44 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$): delta 7.25 (1H, s), 7.02 (2H, d), 6.44 (1H, s), 2.70-2.58 (4H, m), 1.75-1.60 (4H, m), 1.30 (18H, s).
[0172]Example 1 (5)
[Formula 95]



[0173]The title compound which operates it like Example 1 and has the following property value was obtained using the compound manufactured by the reference example 25.
TLC:Rf 0.49 (chloroform: methanol : acetic acid =20:2:1), NMR(CD_3OD): delta 7.12 (1H, s), 6.93 (2H, s), 2.80 (2H, t), 2.54 (2H, t), 1.73-1.52 (4H, m), 1.41 (18H, s).
[0174]example 1 (6)
[Formula 96]

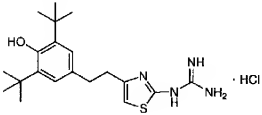


[0175]Using the compound manufactured by the reference example 1, it was operated like the reference example 11 -> reference example 6 -> reference example 7 -> reference example 8 -> example 1, and the title compound which has the following property value was obtained.
TLC:Rf 0.73 (ethyl acetate: acetic acid : water =20:1:1) and NMR($CDCl_3$):delta 7.04 (2H, s),

6.22 (1H, s), 3.67 (3H, s), 2.88 (4H, s), 1.41 (18H, s).

[0176]Example 1 (7)

[Formula 97]



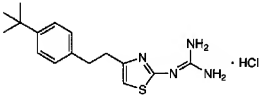
[0177]Using the compound manufactured by the reference example 2, it was operated like the reference example 6 -> reference example 7 -> reference example 8 -> reference example 9 -> example 1, and the title compound which has the following property value was obtained. TLC:Rf 0.78 (ethyl acetate: acetic acid : water =12:2:1) and NMR(DMSO-d_6):delta 8.28-8.25 (4H, m), 6.87 (2H, s), 6.69 (1H, s), 2.84 (4H, s), 1.35 (18H, s).

[0178]Example 1 (8) -1 (11)

Using corresponding aldehyde, it was operated like the reference example 1 -> reference example 6 -> reference example 7 -> reference example 8 -> example 1, and the following compound was obtained.

[0179]Example 1 (8)

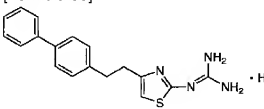
[Formula 98]



[0180]TLC:Rf 0.37 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$+CD_3OD (one drop)): delta 7.33-7.28 (2H, m), 7.12-7.10 (2H, m), 6.47 (1H, s), 2.93 (4H, s), 1.30 (9H, s).

[0181]Example 1 (9)

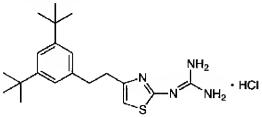
[Formula 99]



[0182]TLC:Rf 0.35 (ethyl acetate: acetic acid : water =20:1:1) and NMR(CD_3OD):delta 7.90-7.25 (9H, m), 6.74 (1H, s), 3.04 (4H, s).

[0183]Example 1 (10)

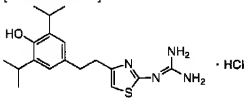
[Formula 100]



[0184]TLC:Rf 0.37 (ethyl acetate: acetic acid : water =20:1:1) and NMR($CDCl_3$):delta 7.26 (1H, s), 7.00 (2H, d), 6.47 (1H, s), 2.94 (4H, s), 1.31 (18H, s).

[0185]Example 1 (11)

[Formula 101]



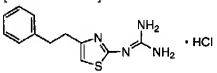
[0186]TLC:Rf 0.39 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$): delta 6.79 (2H, s), 6.47 (1H, s), 5.16 (1H, s), 3.28-3.14 (2H, m), 2.93-2.86 (4H, m), 1.22 (12H, d).

[0187]Example 1 (12) - (20)

Using corresponding carboxylic acid, it was operated like the reference example 8 -> example 1, and the following compound was obtained.

[0188]Example 1 (12)

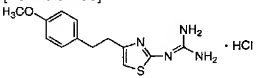
[Formula 102]



[0189]TLC:Rf 0.44 (ethyl acetate: acetic acid : water =20:2:1) and NMR ($CDCl_3$:CD_3OD=20:1):delta 7.31-7.14 (5H, m), 6.33 (1H, s), 3.45 (4H, s).

[0190]Example 1 (13)

[Formula 103]

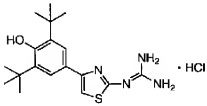


[0191]TLC:Rf 0.43 (ethyl acetate: acetic acid : water =20:2:1) and NMR

($CDCl_3$:CD_3OD=20:1):delta 7.09-6.80 (4H, m), 6.41 (1H, s), 3.79 (4H, s), 2.90 (2H, s).

[0192]Example 1 (14)

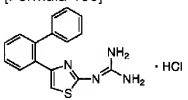
[Formula 104]



[0193]TLC:Rf 0.55 (ethyl acetate: acetic acid : water =20:1:1) and NMR($CDCl_3$):delta 7.58 (2H, s), 6.68 (1H, s), 1.46 (18H, s).

[0194]Example 1 (15)

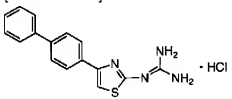
[Formula 105]



[0195]TLC:Rf 0.64 (chloroform: methanol : acetic acid =16:3:1), NMR(DMSO-d_6): delta 12.35 (1H, brs), 7.89 (4H, brs), 7.75 (1H, m), 7.48 (2H, t), 7.34 (4H, m), 7.17 (2H, m), 7.08 (1H, s).

[0196]Example 1 (16)

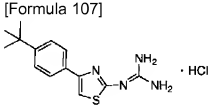
[Formula 106]



[0197]TLC:Rf 0.65 (chloroform: methanol : acetic acid =8:1:1), NMR(DMSO-d_6): delta 12.63 (1H, brs), 8.36 (4H, brs), 8.05 (2H, d), 7.83 (1H, s), 7.74 (4H, m), 7.45 (3H, m).

[0198]Example 1 (17)

[Formula 107]

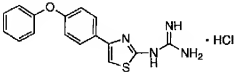


[0199]TLC:Rf 0.76 (chloroform: methanol : acetic acid =16:3:1), NMR(DMSO-d_6): delta 12.58

(1H, brs), 8.34 (4H, brs), 7.85 (2H, d), 7.68 (1H, s), 7.45 (2H,d,J=8Hz), 1.31 (9H, s).

[0200]Example 1 (18)

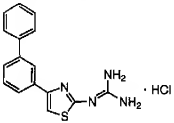
[Formula 108]



[0201]TLC:Rf 0.49 (chloroform: methanol : acetic acid =18:1:1), NMR(DMSO-d_6): delta 12.60 (1H, brs), 8.27 (4H, brs), 7.97 (2H, dd), 7.66 (1H, s), 7.42 (2H, m), 7.18 (2H, m), 7.06 (4H, m).

[0202]Example 1 (19)

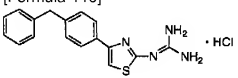
[Formula 109]



[0203]TLC:Rf 0.38 (chloroform: methanol : acetic acid =18:1:1), NMR(DMSO-d_6): delta 12.67 (1H, brs), 8.37 (4H, brs), 8.18 (1H, s), 7.99-7.91 (2H, m), 7.78-7.36 (7H, m).

[0204]Example 1 (20)

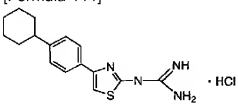
[Formula 110]



[0205]TLC:Rf 0.39 (chloroform: methanol : acetic acid =18:1:1), NMR(DMSO-d_6): delta 12.57 (1H, brs), 8.32 (4H, brs), 7.85 (2H, d), 7.68 (1H, s), 7.34-7.19 (7H, m), 3.98 (2H, s).

[0206]Example 1 (21)

[Formula 111]

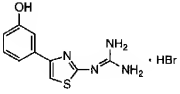


[0207]TLC:Rf 0.40 (chloroform: methanol : acetic acid =18:1:1), NMR(DMSO-d_6): delta 12.67 (1H, brs), 8.37 (4H, brs), 7.85 (2H, d), 7.67 (1H, s), 7.27 (2H, d), 2.51 (1H, m), 1.78 (5H, m),

1.40 (5H, m).

[0208]Example 1 (22)

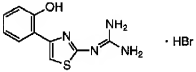
[Formula 112]



[0209]Using the compound manufactured by the reference example 12, it was operated like Example 1 and the title compound which has the following property value was obtained. TLC:Rf 0.51 (chloroform: methanol : acetic acid =15:4:1), NMR(DMSO-d_6): delta 11.99 (1H, brs), 9.52 (1H, s), 8.27 (4H, s), 7.66 (1H, s), 7.27 (3H, m), 6.78 (1H, m).

[0210]Example 1 (23)

[Formula 113]



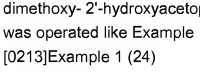
[0211]Using the compound manufactured by the reference example 14, it was operated like Example 1 and the title compound which has the following property value was obtained. TLC:Rf 0.64 (chloroform: methanol : acetic acid =15:4:1), NMR(DMSO-d_6): delta 11.91 (1H, brs), 10.27 (1H, s), 8.23 (4H, s), 7.96 (1H, dd), 7.81 (1H, s), 7.17 (1H, m), 6.93 (2H, m).

[0212]Example 1 (24) - 1 (28)

A 2-bromo-3'-methoxy acetophenone, 4-(chloroacetyl) catechol, Using a 2,3'-dichloro-4' and 6'-dimethoxy- 2'-hydroxyacetophenone, 2-chloroacetophenone, or 2-bromo-2'-acetonaphthone, it was operated like Example 1, respectively and the following compound was obtained.

[0213]Example 1 (24)

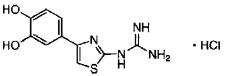
[Formula 114]



[0214]TLC:Rf 0.68 (chloroform: methanol : acetic acid =15:4:1), NMR(DMSO-d_6): delta 11.95 (1H, brs), 8.24 (4H, s), 8.04 (1H, d), 7.77 (1H, s), 7.36 (1H, m), 7.09 (2H, m), 3.93 (3H, s).

[0215]Example 1 (25)

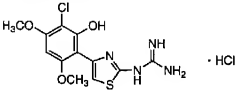
[Formula 115]



[0216]TLC:Rf 0.22 (chloroform: methanol : acetic acid =15:2:1), NMR. (DMSO-d_6) :delta 12.51 (1H,br), 9.25(1H,brs), 9.04(1H,brs), 8.35(4H,brs), 7.39(1H,s), 7.29(1H,d), 7.21(1H,dd), 6.79 (1H,d.

[0217]example 1 (26)

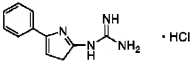
[Formula 116]



[0218]TLC:Rf 0.46 (chloroform: methanol =9:1) and NMR(DMSO-d_6):delta 13.75 (1H, brs), 7.23 (1H, s), 6.49 (4H, brs), 6.36 (1H, s), 3.92 (3H, s), 3.89 (3H, s).

[0219]Example 1 (27)

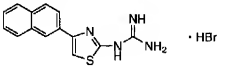
[Formula 117]



[0220]TLC:Rf 0.53 (chloroform: methanol : acetic acid =16:3:1) and NMR(DMSO-d_6):delta 12.68 (1H, brs), 8.36 (4H, s), 7.96 (2H, d), 7.76 (1H, s), 7.50-7.30 (3H, m).

[0221]Example 1 (28)

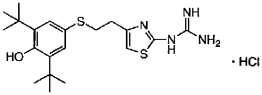
[Formula 118]



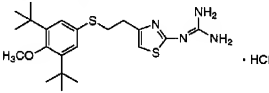
[0222]TLC:Rf 0.60 (chloroform: methanol : acetic acid =16:3:1), NMR(DMSO-d_6): delta 12.04 (1H, brs), 8.55 (1H, s), 8.29 (4H, brs), 8.15-7.85 (5H, m), 7.63-7.45 (2H, m).

[0223]Example 1 (29)

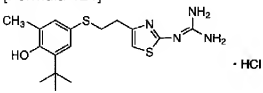
[Formula 119]



[0224]Using the compound manufactured by the reference example 18, it was operated like the reference example 8 and Example 1, and the title compound which has the following property value was obtained.
TLC:Rf 0.62 (ethyl acetate: acetic acid : water =20:1:1) and NMR($CDCl_3$):delta 7.23 (2H, s), 6.44 (1H, s), 3.10 (2H, t), 2.92 (2H, t), 1.42 (18H, s).
[0225]Example 1 (30)
[Formula 120]

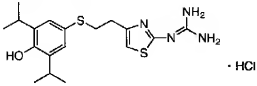


[0226]Using the compound manufactured by the reference example 17, it was operated like the reference example 11 -> reference example 18 -> reference example 8 -> example 1, and the title compound which has the following property value was obtained.
TLC:Rf 0.37 (ethyl acetate: acetic acid : water =20:1:1) and NMR($CDCl_3$):delta 7.24 (2H, s), 6.57 (1H, s), 3.68 (3H, s), 3.15 (2H, t), 2.98 (2H, t), 1.41 (18H, s).
[0227]Example 1 (31) -1 (32)
Using the corresponding compound, it was operated like the reference example 15 -> reference example 16 -> reference example 17 -> reference example 18 -> reference example 8 -> example 1, and the following compound was obtained.
[0228]Example 1 (31)
[Formula 121]



[0229]TLC:Rf 0.41 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$+CD_3OD (one drop)): delta 7.15 (1H, d), 7.00 (1H, d), 6.56 (1H, s), 3.10 (2H, t), 2.90 (2H, t), 2.21 (3H, s), 1.38 (9H, s).
[0230]example 1 (32)

[Formula 122]



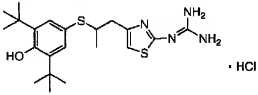
[0231]TLC:Rf 0.43 (ethyl acetate: acetic acid : water =20:1:1) and NMR($CDCl_3$):delta 7.09 (2H, s), 6.54 (1H, s), 3.19-3.07 (4H, m), 2.94-2.85 (2H, m), 1.25 (12H, d).

[0232]Example 1 (33) -1 (34)

Using the compound manufactured by the reference example 16, and the corresponding carboxylic acid derivative, it was operated like the reference example 18 -> reference example 8 -> example 1, and the following compound was obtained.

[0233]Example 1 (33)

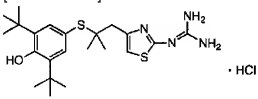
[Formula 123]



[0234]TLC:Rf 0.53 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$): delta 7.25 (2H, s), 6.57 (1H, s), 5.29 (1H, s), 3.33 (1H, m), 2.95 (1H, dd), 2.72 (1H, dd), 1.42 (18H, s), 1.25 (3H, d).

[0235]example 1 (34)

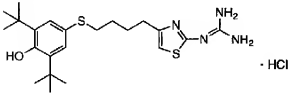
[Formula 124]



[0236]TLC:Rf 0.46 (ethyl acetate: acetic acid : water =20:1:1) and NMR($CDCl_3$):delta 7.33 (2H, s), 6.63 (1H, s), 5.37 (1H, s), 2.85 (2H, s), 1.44 (18H, s), 1.21 (6H, s).

[0237]Example 1 (35)

[Formula 125]



[0238]Using the compound manufactured by the reference example 19, it was operated like the reference example 8 and Example 1, and the title compound which has the following property value was obtained.

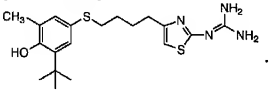
TLC:Rf 0.44 (ethyl acetate: acetic acid : water =20:1:1), NMR(CD_3OD): delta 7.20 (2H, s), 6.71 (1H, s), 2.82 (2H, t), 2.68 (2H, t), 1.81 (2H, m), 1.62 (2H, m), 1.40 (18H, s).

[0239]Example 1 (36) -1 (37)

Using the corresponding compound, it was operated like the reference example 15 -> reference example 16 -> reference example 19 -> reference example 8 -> example 1, and the following compound was obtained.

[0240]Example 1 (36)

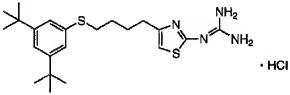
[Formula 126]



[0241]TLC:Rf 0.42 (ethyl acetate: acetic acid : water =20:1:1), NMR. ($CDCl_3$) :. delta 7.17 (1H,d), 7.04(1H,d), 6.43(1H,s), 5.06(1H,s), 2.81(2H,t), 2.61(2H,t), 2.23(3H,s), 1.80-1.56(4H,m), 1.36 (9H, s).

[0242]Example 1 (37)

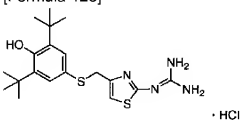
[Formula 127]



[0243]TLC:Rf 0.39 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$): delta 7.24 (1H, d), 7.18 (2H, d), 6.45 (1H, s), 2.95 (2H, t), 2.65 (2H, t), 1.85-1.65 (4H, m), 1.31 (18H, s).

[0244]example 1 (38)

[Formula 128]

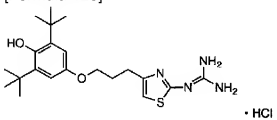


[0245]Using the compound manufactured by the reference example 16, and the corresponding

carboxylic acid derivative, it was operated like the reference example 19 -> reference example 8 -> example 1, and the title compound which has the following property value was obtained.
TLC:Rf 0.57 (chloroform: methanol =10:1) and NMR($CDCl_3$:CD_3OD=10:1):delta 7.14 (2H, s), 6.48 (1H, s), 3.93 (2H, s), 1.39 (18H, s).

[0246]Example 1 (39)

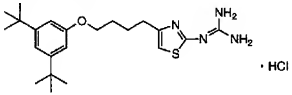
[Formula 129]



[0247]Using the compound manufactured by the reference example 20, it was operated like the reference example 2 -> reference example 7 -> reference example 8 -> reference example 9 -> example 1, and the title compound which has the following property value was obtained.
TLC:Rf 0.35 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$): delta 6.74 (2H, s), 6.32 (1H, s), 3.94 (2H, t), 3.49 (1H, s), 2.79 (2H, t), 2.11 (2H, m), 1.42 (18H, s).

[0248]example 1 (40)

[Formula 130]



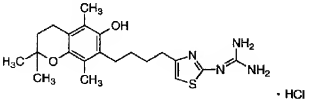
[0249]Using the corresponding compound, it was operated like the reference example 20 -> reference example 7 -> reference example 8 -> example 1, and the title compound which has the following property value was obtained.
TLC:Rf 0.40 (ethyl acetate: acetic acid : water =20:1:1), NMR($CDCl_3$+CD_3OD (one drop)): delta 7.02 (1H, d), 6.75 (2H, d), 6.53 (1H, s), 4.00 (2H, t), 2.72 (2H, t), 1.88-1.80 (4H, m), 1.31 (18H, s).

[0250]Example 1 (41) -1 (43)

The compound written in the PCT application number JP 95/No. 294 specification, The 7-(2-formylethyl)-6-methoxymethyloxy 2, 2, and 5, an 8-tetramethyl chroman, The 5-(2-formylethyl)-6-methoxymethyloxy 2, 2, and 7, an 8-tetramethyl chroman or the 8-(2-formylethyl)-6-methoxymethyloxy 2, 2, and 5, and a 7-tetramethyl chroman are used, It was operated like the reference example 5 -> reference example 6 -> reference example 7 -> reference example 8 -> reference example 9 -> example 1, respectively, and the following compound was obtained.

[0251]Example 1 (41)

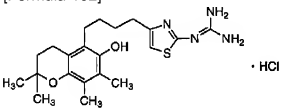
[Formula 131]



[0252]TLC:Rf 0.55 (chloroform: methanol : acetic acid =15:2:1), NMR(CD_3OD): delta 6.75 (1H, s), 2.76-2.53 (6H, m), 2.08 (3H, s), 2.03 (3H, s), 1.85-1.65 (4H, m), 1.60-1.40 (2H, m), 1.24 (6H, s).

[0253]Example 1 (42)

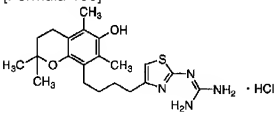
[Formula 132]



[0254]TLC:Rf 0.41 (chloroform: methanol : acetic acid =20:2:1), NMR(CD_3OD): delta 6.75 (1H, s), 2.77-2.53 (6H, m), 2.12 (3H, s), 2.04 (3H, s), 1.85-1.67 (4H, m), 1.60-1.40 (2H, m), 1.26 (6H, s).

[0255]example 1 (43)

[Formula 133]



[0256]TLC:Rf 0.37 (chloroform: methanol : acetic acid =20:2:1), NMR(CD_3OD): delta 6.71 (1H, s), 2.78-2.53 (6H, m), 2.14 (3H, s), 2.09 (3H, s), 1.83-1.60 (4H, m), 1.60-1.38 (2H, m), 1.22 (6H, s).

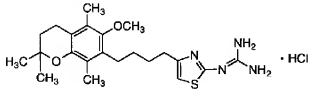
[0257]Example 1 (44) - 1 (46)

The compound which it writes in the PCT application number JP 95/No. 294 specification, or was manufactured using the method of a statement on the specifications, The 7-(2-formylethyl)-6-methoxy- 2, 2, and 5, an 8-tetramethyl chroman, A 5-(2-formylethyl)-6-methoxy-2,2,7,8-tetramethyl chroman or the 8-(2-formylethyl)-6-methoxy- 2, 2, and 5, and a 7-tetramethyl chroman are used, It was operated like the reference example 5 -> reference

example 6 -> reference example 7 -> reference example 8 -> example 1, respectively, and the following compound was obtained.

[0258]Example 1 (44)

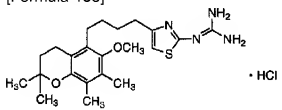
[Formula 134]



[0259]TLC:Rf 0.60 (chloroform: methanol : acetic acid =15:2:1), NMR. (CD_3OD) :. delta 6.73 (1H,s), 3.62(3H,s), 2.78-2.55(6H,m), 2.12(3H,s),2.04(3H,s), 1.86-1.67(4H,m), 1.60-1.40(2H,m), 1.27 (6H, s).

[0260]Example 1 (45)

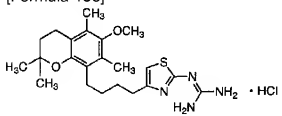
[Formula 135]



[0261]TLC:Rf 0.38 (chloroform: methanol : acetic acid =20:2:1), NMR. (CD_3OD) :. delta 6.76 (1H,s), 3.61(3H,s), 2.78-2.53(6H,m), 2.14(3H,s),2.04(3H,s), 1.83-1.65(4H,m), 1.62-1.38(2H,m), 1.27 (6H, s).

[0262]example 1 (46)

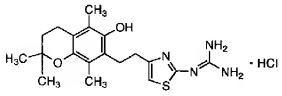
[Formula 136]



[0263]TLC:Rf 0.37 (chloroform: methanol : acetic acid =20:2:1), NMR. (CD_3OD) :. delta 6.69 (1H,s), 3.60(3H,s), 2.75-2.53(6H,m), 2.17(3H,s),2.12(3H,s), 1.83-1.65(4H,m), 1.60-1.38(2H,m), 1.23 (6H, s).

[0264]Example 1 (47)

[Formula 137]

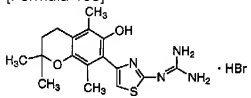


[0265]The 7-(2-methoxy carbonylethyl)-6-methoxymethyloxy 2, 2, and 5 and the 8-tetramethyl chroman which are written in the PCT application number JP 95/No. 294 specification are used, It was operated like the reference example 8 -> reference example 9 -> example 1, and the title compound which has the following property value was obtained.

TLC:Rf 0.43 (chloroform: methanol : acetic acid =15:2:1), NMR. ($CDCl_3$+CD_3OD) :. delta 8.31-8.03(1H,br), 6.74(1H,s), 3.07-2.91(2H,m), 2.91-2.72(2H,m), 2.62(2H,t), 2.12(3H,s), 2.08(3H,s), 1.80 (2H, t), 1.28 (6H, s).

[0266]Example 1 (48)

[Formula 138]

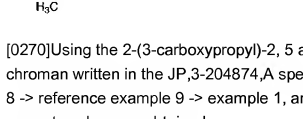


[0267]Using the 7-acetyl-6-methoxymethyloxy 2, 2, and 5 and the 8-tetramethyl chroman which are written in the PCT application number JP 95/No. 294 specification, it was operated like the reference example 10 -> reference example 13 -> reference example 14 -> example 1, and the title compound which has the following property value was obtained.

[0268]TLC:Rf 0.56 (chloroform: methanol : acetic acid =30:4:1), NMR. (DMSO-d_6) :. delta 11.87(1H,brs), 8.17(4H,brs), 7.46(1H,brs), 7.15(1H,brs), 2.61(2H,t,), 2.06(3H,s), 1.87(3H,s), 1.76(2H,t, 1.25 (6H, s).

[0269]example 1 (49)

[Formula 139]

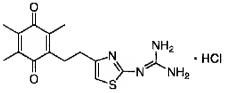


[0270]Using the 2-(3-carboxypropyl)-2, 5 and 7, and 8-tetramethyl 6-methoxymethyloxy chroman written in the JP,3-204874,A specification, it was operated like the reference example 8 -> reference example 9 -> example 1, and the title compound which has the following property value was obtained.

[0271]TLC:Rf 0.42 (ethyl acetate: acetic acid : water =20:2:1), NMR. (DMSO-d_6) :. delta 12.30 (1H,brs), 8.27(4H,brs), 7.37(1H,brs), 6.86(1H,s), 2.59(2H,t), 2.04(3H,s), 2.01(3H,s), 1.97 (3H,s), 1.9-1.6 (4H, m), 1.6-1.3 (2H, m), 1.16 (3H, s).

[0272]Example 1 (50)

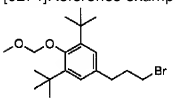
[Formula 140]



[0273]Using the compound manufactured by the reference example 21, it was operated like the reference example 8 -> example 1, and the title compound which has the following property value was obtained.

TLC:Rf 0.51 (ethyl acetate: acetic acid : water =12:2:1), NMR(DMSO-d_6): delta 12.44 (1H, brs), 8.29 (4H, brs), 6.93 (1H, s), 2.9-2.6 (4H, m), 1.95 (6H, s), 1.84 (3H, s).

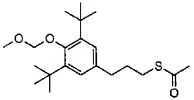
[0274]Reference example 26 [Formula 141]



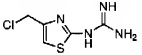
[0275]. Manufactured like the reference example 6 using the compound manufactured by the reference example 3. Triphenyl phosphine (1.57g), sodium bicarbonate (1.26g), and carbon tetrabromide (2.49g) were added to the methylene chloride solution (50 ml) of 3-(3,5-di-t-butyl-4-methoxymethyloxy phenyl) propanol (1.53g). The mixture was agitated at the room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, saturated sodium bicarbonate, water, and a saturation salt solution washed one by one, and it condensed after desiccation with magnesium sulfate. The filtrate obtained by hexane-ethyl acetate washing a residue was condensed. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:10), and the title compound (1.46g) which has the following property value was obtained.

TLC:Rf 0.58 (ethyl acetate: n-hexane =1:10).

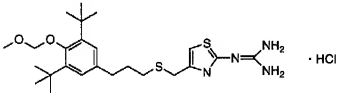
[0276]Reference example 27 [Formula 142]



[0277]Thiacetic acid sodium (676 mg) was added to the acetone solution (10 ml) of the compound (1.46g) manufactured by the reference example 26. The mixture was flowed back for 4 hours. It flowed into water after cooling a reaction solution, and ethyl acetate extracted. Water and a saturation salt solution washed the organic layer, and it condensed after desiccation with sodium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:30), and the title compound (1.45g) which has the following property value was obtained.
TLC:Rf 0.38 (ethyl acetate: n-hexane =1:10).
[0278]Reference example 28 [Formula 143]



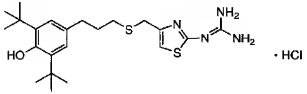
[0279]The acetone solution (6 ml) of 1,3-dichloroacetone (1.8g) was added to the acetone suspension (7.5 ml) of amidino thiourea (1.68g). The mixture was agitated at the room temperature overnight. Acetone washed the precipitated crystal, it recrystallized in ethanol, and the title compound (1.61g) which has the following property value was obtained.
TLC:Rf 0.60 (chloroform: methanol : acetic acid =15:2:1).
[0280]Reference example 29 [Formula 144]



[0281]It agitated until it added sodium (46 mg) to ethanol (5 ml) little by little under argon and dissolved in it. The ethanol solution (5 ml) of the compound (366 mg) manufactured by the reference example 27 was added to the ethanol solution of the prepared ethoxysodium under 0 ** and argon. The mixed solution was agitated for 30 minutes at 0 **. The ethanol solution (5 ml) of the compound (114 mg) manufactured by the reference example 28 was slowly dropped at the reaction solution. The mixed solution was agitated at the room temperature for 3 hours. The ethanol solution (5 ml) of the compound (100 mg) manufactured by the reference example 28 was dropped. The mixed solution was agitated at the room temperature for 16 hours. The sludge was filtered out and the filtrate was condensed. The residue was refined by column chromatography (chloroform: methanol =30:1->10:1), and the title compound (480 mg) which has the following property value was obtained.
[0282]TLC:Rf 0.85 (chloroform: methanol : acetic acid =15:2:1), NMR. ($CDCl_3$) :delta 7.04 (2H,s),6.33(1H,s), 4.88(2H,s), 3.63(3H,s), 2.63(2H,t), 2.53(2H,t), 1.88(2H,quint), 1.78-1.55(2H,

br, 1.43 (18H, s).

[0283]Example 2 [Formula 145]



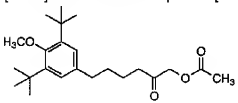
[0284]The compound (450 mg) manufactured by the reference example 29 was operated like the reference example 9, and the title compound (408 mg) which has the following property value was obtained.

TLC:Rf 0.30 (chloroform: methanol =10:1), NMR. (DMSO-d_6) :delta 12.85(1H,br), 8.35(3H,brs), 6.95(1H,s), 6.88(1H,s), 6.70(1H,s), 3.73(2H,s), 2.60-2.43(2H,m), 1.35(18H,s.

[0285]Reference example 30 [Formula 146]

[0286]Water (80 ml) and palladium (IV) acetate (5.1g) were added to the THF solution (80 ml) of 2,3,5-trimethyl hydroquinone (1.52g). Heating flowing back of the mixture was carried out for 30 minutes. 2N sodium hydroxide was added to the reaction mixture, and ether extracted. Water and a saturation salt solution washed the organic layer, it condensed after desiccation with magnesium sulfate, and the title compound (1.32g) was obtained.

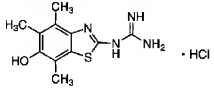
[0287]Reference example 31 [Formula 147]



[0288]. Manufactured like the reference example 7 and the reference example 8 using the compound manufactured by the reference example 11. The acetone solution (10 ml) of 6-(3,5-di-t-butyl-4-methoxypheny)-alpha-chloro-2-hexanone (200 mg) and potassium acetate (111 mg) was agitated at 65 ** for 17 hours. The reaction solution was condensed and it diluted with ethyl acetate. Water and a saturation salt solution were washed, the organic layer was condensed after desiccation with magnesium sulfate, and the title compound (1.32g) which has the following property value was obtained.

TLC:Rf 0.33 (hexane: ethyl acetate =5:1).

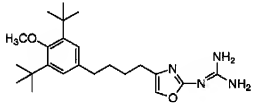
[0289]Example 3 [Formula 148]



[0290]Concentrated hydrochloric acid (0.134 ml) was added to the ethanol solution (10 ml) of guanidyl thiourea (520 mg). The ethanol solution (20 ml) of the compound (1.32g) manufactured by the reference example 30 was added to the mixture. The mixture was agitated for two days at the room temperature. The reaction mixture was filtered and the crystal was washed by acetonitrile. The filtrate was condensed and the residue was recrystallized with ethanol and ether. Acetonitrile, ethanol, and ether washed the precipitated crystal one by one, it dried and the title compound (254 mg) which has the following property value was obtained.

[0291]TLC:Rf 0.18 (chloroform: methanol =5:1) and NMR(DMSO-d_6):delta 12.6 (1H, brs), 8.51 (1H, s), 8.37 (4H, s), 2.47 (3H, s), 2.30 (3H, s), 2.21 (3H, s).

[0292]Example 4 [Formula 149]



[0293]The 5N solution of hydrochloric acid (1.8 ml) was added to the compound (170 mg) manufactured by the reference example 31, and the dioxan solution (9 ml) of dicyandiamide (380 mg), and it condensed after 20-hour churning at the room temperature. The residue was refined by column chromatography (ethyl acetate : 1:10 ->5:1 -> n-hexane = chloroform : methanol =30:1->10:1), and the title compound (51 mg) which has the following property value was obtained.

[0294]TLC:Rf 0.50 (chloroform: methanol =9:1) and NMR($CDCl_3$):delta 7.03 (2H, s), 6.92 (1H, s), 5.95 (4H, brs), 3.67 (3H, s), 2.55 (2H, t), 2.45 (2H, t), 1.67 (4H, m), 1.42 (18H, s).

[0295]

[Example(s) of Production]

It tableted, after mixing each one or less example [of pharmaceutical preparation] ingredient with a conventional method, and 100 doses of tablets which have a 50-mg active ingredient in 1 dose were obtained.

- 4-(4-(3,5-di-t-butyl-4-hydroxyphenyl) butyl)-2-guanidyl thiazole -- 5.0g and calcium carboxymethyl cellulose (disintegrator) -- 0.2g and magnesium stearate (lubricant) -- 0.1g and

microcrystalline cellulose -- 4.7g[0296]After mixing each two or less example [of pharmaceutical preparation] ingredient with a conventional method, the solution was sterilized with the conventional method, and it filled up the ampul with 5 ml at a time, and freeze-dried with the conventional method, and 100 ampuls which contain a 20-mg active ingredient among 1 ampul were obtained.

- 4-(4-(3,5-di-t-butyl-4-hydroxyphenyl) butyl)-2-guanidyl thiazole -- 2.0g and mannitol -- 200 mg and distilled water -- 500 ml

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[Translation done.]